Value-based decision making and alcohol use disorder

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Wertbasierte Entscheidungsprozesse und Alkoholkonsumstörungen

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Vorwort

Bei der vorliegenden Arbeit handelt es sich um eine publikationsbasierte Dissertation. Sie wurde gemäß § 8 (1) der Promotionsordnung vom 23.02.2011 (zuletzt geändert am 18.06.2014) der Fakultät Mathematik und Naturwissenschaften an der Technischen Universität Dresden als abgeschlossene Einzelarbeit verfasst.

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Studie 1 – Ich entwickelte unter Supervision von Prof. Michael N. Smolka die Fragestellung, führte die Auswertung der Verhaltens- und Bildgebungsdaten aus, interpretierte die Ergebnisse und erstellte das Manuskript einschließlich aller Abbildungen.

Studie 2 – Ich war an der Interpretation der Verhaltens- und Bildgebungsdaten und der kritischen Revision des Manuskriptes beteiligt.

Studie 3 – Ich entwickelte gemeinsam mit Dr. Nadine Bernhardt unter Supervision von Prof. Michael N. Smolka die Fragestellung, führte die statistische Auswertung durch, interpretierte die Ergebnisse und erstellte das Manuskript einschließlich aller Abbildungen.

Die Dissertation wurde vollständig in englischer Sprache verfasst, um Einheitlichkeit zu den publizierten Artikeln zu gewährleisten.

Während meiner Tätigkeit als Doktorand bei Prof. Dr. Michael N. Smolka sind vier weitere inhaltlich verwandte wissenschaftliche Artikel entstanden, die bereits veröffentlicht sind und bei denen ich Koautor bin. Bei diesen Arbeiten war ich an der Erhebung der Daten beteiligt, habe die Interpretation der Ergebnisse unterstützt und die Manuskripte kritisch revidiert.

Sebold, M., Deserno, L., Nebe, S., Schad, D. J., Garbusow, M., Hägele, C., Keller, J., Jünger, E., Kathmann, N., Smolka, M. N., Rapp, M. A., Schlagenhauf, F., Heinz, A., & Huys, Q. J. M. (2014). Model-based and model-free decisions in alcohol dependence. *Neuropsychobiology, 70*(2), 122-131. doi: 10.1159/000362840

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Sebold, M., Schad, D. J., Nebe, S**.**, Garbusow, M., Jünger, E., Kroemer, N. B., Kathmann, N., Zimmermann, U. S., Smolka, M. N., Rapp, M. A., Heinz, A., & Huys, Q. J. M. (2016). Don't Think, Just Feel the Music: Individuals with Strong Pavlovian-to-instrumental Transfer Effects Rely Less on Model-based Reinforcement Learning. *Journal of Cognitive Neuroscience,28*(7), *985-995*. doi: 10.1162/jocn_a_00945

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Die Ergebnisse dieser Arbeiten sind nicht Teil dieser Dissertation, fließen aber in die allgemeine Diskussion der Forschungsergebnisse der in den Kapiteln 2 bis 4 dargestellten Studien ein.

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List of Abbreviations

ACC	Anterior cingulate cortex
ADS	Alcohol Dependence Scale
AEQ	Alcohol Expectancy Questionnaire
ALT	Alanine transaminase
ANOVA	Analysis of variance
APA	American Psychiatric Association
AST	Aspartate transaminase
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorder Identification Test
BIS-15	Barratt Impulsiveness Scale, short form
BOLD	Blood-oxygen level-dependent
CIDI	Composite International Diagnostic Interview
CIWA	Clinical Institute Withdrawal Assessment for Alcohol Scale
dACC	Dorsal anterior cingulate cortex
DALYs	Disability-adjusted life years
DD	Delay Discounting
dlPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
DSbw	Digit span backwards
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
EPI	Echo-planar imaging
EU	European Union
FDR	False Discovery Rate
FHAM	Family History Assessment Module
fMRI	Functional Magnetic Resonance Imaging
FTQ	Family Tree Questionnaire
FU	Follow-up
γ-GT	Gamma-glutamyl transferase
HED	Heavy episodic drinking
IGT	Iowa Gambling Task
L-DOPA	Levodopa (L-3,4-dihydroxyphenylalanine)
LeAD	Learning and Alcohol Dependence
M	Mean
MANOVA	Multivariate analysis of variance
Mdn	Median
MG	Mixed-gambles task
MNI	Montreal Neurological Institute
mPFC	Medial prefrontal cortex
MPRAGE	Magnetization-prepared rapid gradient echo
MWT-B	Mehrfachwahl-Wortschatztest Version B
NAcc	Nucleus accumbens

OCDS-G	Obsessive Compulsive Drinking Scale (German version)
OFC	Orbitofrontal cortex
PD	Probability Discounting
PDG	Probability Discounting for Gains
PDL	Probability Discounting for Losses
PEth	Phosphatidylethanol
PIT	Pavlovian-instrumental transfer
PFC	Prefrontal cortex
RL	Reinforcement learning
ROI	Region of interest
RPE	Reward prediction error
$RPE_{\Delta MB}$	Difference between model-free and model-based reward prediction errors
RPE_{MF}	Model-free reward prediction error
SARSA	State-action-reward-state-action
SD	Standard deviation
SES	Socioeconomic status
SN	Substantia nigra
SPM	Statistical Parametric Mapping
SVC	Small volume correction
SUD	Substance use disorder
SURPS	Substance Use Risk Profile Scale
TD	Temporal difference
TE	Echo time
TMT	Trail Making Test
TR	Repetition time
UFA	Unified framework for addiction
USA	United States of America
VBDM	Value-based decision making
vmPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area
WHO	World Health Organization

King Alcohol and the Prime Minister

John Warner Barber, ca. 1820-1880

Abstract

Alcohol use disorder (AUD) is a widespread mental disease denoted by chronic alcohol use despite significant negative consequences for a person's life. It affected more than 14 million persons in Europe alone and accounted for more than 5% of deaths worldwide in 2011-2012. Understanding the psychological and neurobiological mechanisms driving the development and maintenance of pathological alcohol use is key to conceptualizing new programs for prevention and therapy of AUD. There has been a variety of etiological models trying to describe and relate these mechanisms. Lately, the view of AUD as a disorder of learning and decision making has received much support proposing dual systems to be at work in AUD – one system being deliberate, forward-planning, and goal-directed and the other one reflexive, automatic, and habitual. Both systems supposedly work in parallel in a framework of value-based decision making and their balance can be flexibly adjusted in healthy agents, while a progressive imbalance favoring habitual over goal-directed choice strategies is assumed in AUD. This imbalance has been theoretically associated to neural adaptations to chronic alcohol use in corticostriatal pathways involved in reward processing, especially in ventral striatum. However, these theoretical models are grounded strongly on animal research while empirical research in the human domain remains rather sparse and inconclusive. Furthermore, alterations in value-based decision-making processes and their neural implementation might not only result from prolonged alcohol misuse but may also represent premorbid interindividual differences posing a risk factor for the development of AUD.

Therefore, I here present three studies investigating the relation of alcohol use with the balance between goal-directed and habitual decision systems and with parameters modulating option valuation processes of these systems, namely delay, risk, and valence of option outcomes. To separate the investigation of these decision processes as predisposing risk for or consequence of alcohol use, two samples were examined: one sample of 201 eighteen-year-old men being neither abstinent from nor dependent on alcohol as well as one sample of 114 AUD patients in detoxification treatment and 98 control participants matched for age, sex, educational background, and smoking status. Both samples had a baseline assessment of several behavioral tasks, questionnaires, and neuropsychological testing and were followed-up over one year to examine drinking trajectories in the sample of young men and relapse in detoxified patients. The behavioral tasks included a sequential choice task using model-free and model-based reinforcement learning as operationalization of habitual and goal-directed

decision making, respectively, during functional magnetic resonance imaging and four tasks probing participants' delay discounting, probability discounting for gains and losses, and loss aversion.

Study 1 presents the cross-sectional analysis of the sequential choice task in relation to baseline drinking behavior of the young-adult sample. These analyses did not reveal an association between non-pathological alcohol use and habitual and goal-directed control on neither a behavioral nor neural level except for one exploratory finding of increased BOLD responses to model-free habitual learning signals in participants with earlier onset of drinking. Study 2 examined the same task in AUD patients compared to control participants showing no difference in behavioral control or neural correlates between those groups. However, prospectively relapsing AUD patients showed lower BOLD responses associated to model-based goal-directed control than abstaining patients and control participants. Additionally, the interaction of goal-directed control and positive expectancies of alcohol effects discriminated subsequently relapsing and abstaining patients revealing an increased risk of relapse for those patients who showed higher levels of goal-directed control and low alcohol expectancies or low levels of goal-directedness and high expectancies. Study 3 examined modulating features of goal-directed and habitual option valuation – delay, risk, and valence of options – in association to alcohol use in the young-adult sample and AUD status in the sample of patients and matched control participants on a cross-sectional as well as longitudinal level. This study revealed no relation of delay, risk, and loss aversion with current alcohol use and consumption one year later in the young men. In contrast, AUD patients showed systematically more impulsive choice behavior than control participants in all four tasks: a higher preference for immediate rewards, more risky choices when facing gains and less when facing losses, and lower loss aversion. Furthermore, a general tendency to overestimate the probability of uncertain losses could predict relapse risk over the following year in AUD patients.

Taken together, these results do not support the hypothesis that mechanisms of value-based decision making might be predisposing risk factors for alcohol consumption. The findings for patients already suffering from AUD are mixed: while choice biases regarding delays, risks, and valence of option outcomes seem to be altered systematically in AUD, there was no indication of an imbalance of habitual and goal-directed control. These findings challenge the assumption of a generalized outcome-unspecific shift of behavioral control from goal-directed to habitual strategies during the development of AUD and point towards several possible future avenues of research to modify or extend the theoretical model.

Chapter 1. Perspectives on alcohol use disorder

My thesis investigates cognitive accounts of alcohol use disorder and mechanisms of learning, decision making, and behavioral control associated with alcohol use. In this chapter, I introduce the concept of alcohol use disorders including its size and burden for human society. Furthermore, I give an overview on psychological perspectives on alcohol use, especially regarding value-based decision-making processes and dual-system approaches of goal-directed and habitual control. Finally, I explain a neurobiological perspective on alcohol use disorders, where I focus in particular on reward-processing and its relation to behavioral control.

1.1 The size of alcohol use disorder

1.1.1 Terminology of alcohol-use related disorders

There are several terms regarding risky, harmful, or pathological alcohol use found in the literature, e.g. alcoholism, alcohol abuse or misuse, alcohol dependence, alcohol addiction, and alcohol use disorder. Accompanying this variety of terms is an ongoing debate about the definitions, relations, similarities, and differences between these concepts (Robinson & Berridge, 1993; Volkow & Baler, 2014). Moreover, key organizations in researching alcohol use like the World Health Organization (WHO), American Psychiatric Association (APA), or the National Institute on Alcohol Abuse and Alcoholism take into account psychological effects of the terms to avoid stigmatization of affected persons. For this reason, there has been a recent change in nomenclature in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5; American Psychiatric Association, 2013). While the previous edition distinguished between the diagnoses alcohol abuse and alcohol dependence to classify persons with milder and more severe patterns of alcohol consumption, respectively, the latest edition of the DSM subsumes both diagnoses under the term alcohol use disorder (AUD). The authors of the DSM-5 define the following criteria for AUD:

A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

A. Alcohol is often taken in larger amounts or over a longer period than was intended.
B. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.

C. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
D. Craving, or a strong desire or urge to use alcohol
E. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
F. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
G. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
H. Recurrent alcohol use in situations in which it is physically hazardous.
I. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
J. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of alcohol.
K. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for alcohol.
    b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

This list comprises all seven symptoms constituting the previously used diagnosis of alcohol dependence (A-C, G, I-K), three of four symptoms of the previous diagnosis of alcohol abuse (E, F, H), and the additional symptom of craving (D). Meeting at least two of these criteria in the same 12-month interval, one can be diagnosed with AUD. The number of fulfilled criteria determines the severity of AUD, from mild (2-3 symptoms) over moderate (4-5) to severe (6+). With this list of symptoms, AUD includes all syndromes being referred to as alcohol addiction, abuse and dependence and refers to physiological as well as psychological phenomena related to pathological alcohol use.

1.1.2 Size and burden of alcohol consumption and alcohol use disorders

Alcohol use disorders have been estimated to be the fourth most prevalent mental disorder in Europe in 2011 affecting 3.4% of the population aged 15 years or older corresponding to 14.6 million persons (referring to the DSM-IV diagnosis of alcohol dependence; Wittchen et al., 2011)[1]. In the USA, the 12-month and lifetime prevalence estimates for an AUD (based on DSM-5) were 13.9% and 29.1%, respectively, in 2012-2013 (Grant et al., 2015). However, it is not only when suffering from AUD that alcohol consumption poses a health risk. Alcohol intake can already have detrimental effects on health when being consumed at low to moderate levels.

In 2014, the WHO published the "Global status report on alcohol and health" providing information about the global and local levels of alcohol consumption and its health consequences (World Health Organization, 2014). According to this report, the average human had consumed 6.2 l of pure alcohol in 2010 resulting in an average intake of 13.5 g alcohol per day, while 61.7% of the very same population were abstinent from alcohol in the past year (World Health Organization, 2014). But levels of alcohol use and abstention vary greatly by geographical and cultural region; for example, inhabitants of the WHO European Region (ranging from Iceland and Portugal in the West to the Russian Federation and Kyrgyzstan in the East) had an average per capita alcohol consumption of 10.9 l in 2010. Although this region is inhabited by only 14.7% of the world's population, it accounts for 25.7% of the globally consumed alcohol. Meanwhile, the per capita alcohol consumption in the WHO Eastern Mediterranean Region was 0.7 l, a result of the very high abstention rate of 94.6% in the past 12 months (World Health Organization, 2014).

Another report on "Public health successes and missed opportunities" demonstrated the "Trends in alcohol consumption and attributable mortality in the WHO European Region" from 1990 to 2014 (World Health Organization, 2016). This publication reported that the alcohol consumption per capita in the European region has slightly decreased over the past 25 years (-10.8%, from 12.0 l pure alcohol per capita in 1990 to 10.7 l in 2014). Shrinking the focus on central-western countries of the European Union reveals an even stronger decrease (-21.7%, from 14.3 l in 1990 to 11.2 l in 2014). However, alcohol consumption in Europe is still the highest compared to all other WHO regions and it poses a serious threat to the well-being of our society.

[1] Please note that all epidemiological information about alcohol consumption, disease burden, and prevalence in this section regard the population aged 15 years or older if not stated otherwise.

Consumption of alcohol is one of the top five risk factors for disease, disability, and death and has shown to be causal for over 200 disease and injury conditions (World Health Organization, 2014). In 2012, alcohol use accounted for 5.9% of all deaths worldwide amounting to 3.3 million fatalities (World Health Organization, 2014). Therefore, alcohol consumption is "one of the most important risk factors for disease" (World Health Organization, 2016; p.1). Harmful alcohol use has been shown to be causal for liver cirrhosis, various types of cancer, cardiovascular diseases, and intentional and unintentional injuries (World Health Organization, 2016). In Germany, 6.2% of the population between 18 and 64 years of age suffered from some clinical disorder attributed to alcohol consumption in 2006, corresponding to more than 3 million affected persons (Kraus, Piontek, Pabst, & Bühringer, 2011). Clinical disorders attributable to alcohol have led to 334,000 hospitalizations in Germany in 2008 (Kraus et al., 2011). The harmful potential of alcohol consumption is composed of three characteristics: the quality of consumed beverages, the volume and the pattern of consumption (World Health Organization, 2014). First, the quality of the consumed alcoholic beverages primarily plays a role if consuming informally or illegally produced drinks, as those have an increased probability of being contaminated with methanol, toxic metals or ethyl carbamate (Rehm, Kanteres, & Lachenmeier, 2010; World Health Organization, 2014). Second, the volume of consumed alcohol is mostly positively associated with the risk for those diseases that are caused (at least in part) by alcohol (International Agency for Research on Cancer & World Health Organization, 2010). For example, the relative risk for cancer of the oral cavity is increased by 76% with a daily consumption of 25 g alcohol, which corresponds to two small bottles (330 ml) of regular beer (4.8 Vol% alcohol) compared to abstinence from alcohol, and increases to being more than six-fold with an average daily intake of 100 g alcohol (Bagnardi, Blangiardo, Vecchia, & Corrao, 2001). Third, heavy episodic drinking (HED), defined by consuming at least 60 g alcohol per drinking occasion at least once per month, is associated with detrimental health consequences even if the person has a low average alcohol intake. HED occurred in 16.5% of the population of the WHO European Region, but has a higher prevalence of 31.2% in the subgroup of 15- to 19-year-olds (World Health Organization, 2014).

This shows the relevance of age as an important covariate in describing the risk of alcohol consumption. Children, adolescents, and the elderly are generally subject to increased harm by the same amount of alcohol consumed than any other age group (World Health Organization, 2014). Another important factor of influence on alcohol use is the sex as females generally show increased rates of abstention from alcohol, decreased per capita

consumption, decreased rates of HED (International Agency for Research on Cancer & World Health Organization, 2010; World Health Organization, 2014) and decreased risk of suffering from AUD (Wittchen et al., 2011). A third important risk factor for harmful alcohol use is a family history of AUD (World Health Organization, 2014). Having a parent suffering from AUD increases the lifetime risk of developing AUD four- to eight-fold (Zimmermann, Blomeyer, Laucht, & Mann, 2007), which together with twin and adoption studies has led to the estimation of complex genetic factors accounting for 40-60% of the risk to develop AUD (American Psychiatric Association, 2013; Schuckit, 2009; Zimmermann et al., 2009). Furthermore, per capita consumption of alcohol, prevalence of current drinking, and HED were correlated with the economic wealth of a country with higher rates of consumption being found in higher income countries (World Health Organization, 2014). Last, there is also an association between socioeconomic status (SES) and alcohol consumption. Studies have found that higher SES corresponds to smaller abstention rates, more drinking occasions, and more drinkers with low-risk consumption patterns, whereas persons of lower SES may drink less but still have higher rates of harmful consequences of drinking (International Agency for Research on Cancer & World Health Organization, 2010; World Health Organization, 2014). This seeming contradiction might be resolved with the notion that members of low SES groups lack the social and economic resources to avoid aversive consequences of alcohol use (World Health Organization, 2014), have a higher prevalence of HED, or more often drink alcohol in rather unsafe or violent environments (World Health Organization, 2010).

Due to its detrimental effects on health and its addiction potential, alcohol consumption also has an economic burden for societies. In 2012, 5.1% of the global burden of disease and injury was associated with alcohol use and its consequences (World Health Organization, 2014). This was measured in disability-adjusted life years (DALYs). Alcohol-related DALYs represent the years of life that are lost due to premature death or living with a disability in consequence of alcohol use. In Germany, alcohol-related DALYs were estimated to amount to 392,000 years in 2004 (Kraus et al., 2011). Global estimates of the leading risk factors for DALYs see alcohol use on third place accounting for 4.5% of world-wide DALYs in 2004 corresponding to 69 million years of healthy life lost due to premature death or living in disability (World Health Organization, 2009). The direct (e.g. costs occurring due to hospitalization and treatment, unemployment and welfare systems, or encounters with the police and justice system) and indirect (e.g. lost economic productivity caused by unemployment, decreased individual work force, or absenteeism) social and economic costs

of alcohol use were estimated to sum up to 125 billion Euros in the EU in 2003 or 233.5 billion US Dollars in the USA in 2006 (World Health Organization, 2014).

In summary, alcohol consumption is a risk factor for the diminishment of individual and societal well-being. The period of late adolescence and young adulthood is associated with increased HED, especially in young men, which in turn is associated with more severe drinking trajectories and adverse health outcomes due to alcohol consumption. Though alcohol consumption has slightly decreased in many regions of the world in the past decades, above all in the western industrialized countries, the global burden of alcohol use and its harmful consequences is by no means lifted from our shoulders. This makes it all the more important to understand the mechanisms of the development and maintenance of AUD, because only detailed knowledge of its etiology can guide us in developing well-functioning programs for prevention and therapy of AUD.

1.2 Cognitive psychological perspectives on alcohol use disorder

1.2.1 A unified framework for addiction

As we have seen in the previous section, alcohol use and its related disorders are a serious threat to societies and a burden for the global community. But many researchers have accepted the challenge of trying to understand the development and maintenance of AUD. In the last decades, numerous theories have been proposed concerning substance use disorders (SUDs). These theories often treated all substances of abuse equally, presumably because there are many similarities between their respective effects on a behavioral and neural-circuit level. Most influential in the past decades were theories of incentive sensitization (Robinson & Berridge, 1993), impulsivity (Ainslie, 1992, as cited in Redish, Jensen, & Johnson, 2008), opponent processes (Koob & Le Moal, 1997; Solomon & Corbit, 1973), neural adaptations (Volkow, Fowler, & Wang, 2003), non-compensable dopamine (Di Chiara, 1999; Redish, 2004), and an imbalance between dual systems (Bechara, 2005; Bickel et al., 2007; Robbins & Everitt, 1999; Tiffany, 1990). All of those have proven to explain some but not all features of SUDs (Redish et al., 2008). Redish, Jensen, and Johnson (2008) delivered a critical review of previous etiology models of SUDs and attempted to unify them into one overarching theory – the unified framework for addiction (UFA). These authors defined SUDs as a spectrum disorder and postulated that all previous theories had the commonality of proposing some influence on the processing of values or costs associated with the seeking and taking of drugs. In their view and in line with many of the previous approaches, SUDs can be classified as

disorders of decision making (Redish, 2004; Redish et al., 2008). This means that people suffering from SUDs repeatedly make suboptimal choices – they decide to use a drug of abuse despite the known negative long-term consequences of this choice. However, this does not necessarily mean that affected persons willingly ignore the costs of substance use. Rather, the evaluation of choice options at hand is altered or the action selection process based on this evaluation goes awry (Rangel, Camerer, & Montague, 2008). Furthermore, Redish, Jensen, and Johnson (2008) revealed an underlying structural commonality: all of the previous, influential theories about SUD etiology could be conciliated in a model of two separate yet interacting systems – one being "a flexible, cognitive, planning" and the other "a rigid, automatic, habit-based system" (Redish et al., 2008; p. 418). These two systems or variations of them have a long history in psychology, as they are supposedly the same as the ones proposed by various past dual system accounts, e.g. cognitive map vs. route systems in the animal navigation (e.g. O'Keefe & Nadel, 1978), declarative vs. procedural (e.g. N. J. Cohen & Squire, 1980; Redish, 1999) or explicit vs. implicit learning systems in the human learning (e.g. Schacter, 1987), and controlled vs. automatic processes in the behavioral control literature (Schneider & Shiffrin, 1977; Shiffrin & Schneider, 1977). Apart from its application in the UFA, dual-system accounts proposing a cognitive goal-directed and an automatic habitual mechanism have received much attention in the past years in learning and decision-making research (see section 1.2.3). In response to the critique of their peers, Redish, Jensen, and Johnson (2008) expanded their framework to include a Pavlovian/affective system. This system acts through an initial emotional response, which then triggers a "pre-wired" Pavlovian conditioned behavioral response.

In their seminal work, Redish, Jensen, and Johnson (2008) suggested ten vulnerability factors or failure points in decision-making processes, which lead to suboptimal decisions and actions and, consequently, to the development of SUDs. These factors include among other things the overvaluation of the expected value of an outcome, changes in the homeostatic set point or in learning processes, inhibition of the planning system favoring habitual decision making, and over-fast discounting processes. As they proposed multiple vulnerabilities, which could co-exist or interact, the authors of the UFA also suggested that there are multiple pathways to SUDs and, hence, various addiction syndromes (Ahmed, 2008). This complexity made certain that every person suffering from SUDs could be found in the UFA with her individual pattern of maladaptive decision-making.

Various scientists from the field of addiction research responded to the proposed UFA commending or criticizing it and proposing changes or extensions (e.g. Bickel & Yi, 2008;

Chambers, 2008; Goudie, Field, & Cole, 2008; Hart & Krauss, 2008; Moal, 2008; Ostlund & Balleine, 2008). Some of them suggested trying to narrow it down even further: interactions between vulnerabilities in the UFA should be identified, which could lead to certain clinical features of addiction; single vulnerabilities should be examined further to check whether they are historically grown as different constructs but meaning the same or at least very close constructs; and processes should be weighted in order to find those being more relevant than others for development, maintenance, and treatment of SUDs (Bickel & Yi, 2008; Goudie et al., 2008). Moreover, Redish, Jensen, and Johnson (2008) argue for the UFA almost exclusively from a neurophysiological point of view – most failure points are based on the pharmacological mechanisms and neurobiological adaptions consequent to drug consumption. Meanwhile, certain aspects being associated with the etiology of SUDs were missing in the UFA, for example neurodevelopmental dynamics (Ahmed, 2008) and the influence of social and sociocultural (Boden, 2008; Hart & Krauss, 2008; Lende, 2008), affective (Kiviniemi & Bevins, 2008; Moal, 2008), environmental (Neal & Wood, 2008), and psychological factors (Neal & Wood, 2008; Ostlund & Balleine, 2008; Sarnecki, Traynor, & Clune, 2008; Wiers, Havermans, Deutsch, & Stacy, 2008).

However, by and large, Redish, Jensen, and Johnson (2008) were commended for their important work trying to take the loose threads of various models for SUD etiology and to unite them in one framework, but clearly there are still many gaps in our knowledge about altered choice in SUDs to be filled. All the vulnerability factors proposed in the UFA are failures in decision-making based on subjective values and costs of choice options. In order to investigate the possible vulnerabilities further, a more detailed model of decision-making mechanisms in general is needed. Therefore, I will introduce a theoretical framework of value-based decision making next.

1.2.2 Value-based decision making

Theories of value-based decision making (VBDM) consider the processes involved in the gathering and integration of information to choose between possible actions in a given state and acting according to the result of this process by any agent – be it animal, human, or (artificially intelligent) machine [2]. Five basic processes have been suggested to be comprised

[2] This process model is assumed to be valid in animals as well as humans and has also been used in machine learning and artificial intelligence research. Due to this universality, I will use the abstract term agent in the forthcoming descriptions.

in VBDM (Rangel et al., 2008), which are closely connected and build a circular model of behavioral control (see Figure 1).

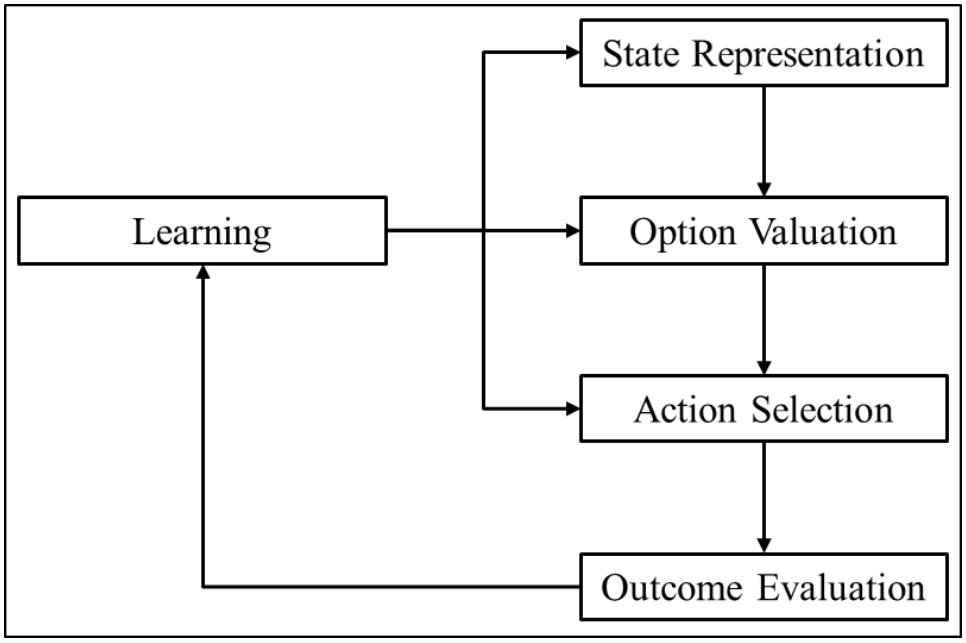

Figure 1. Framework of value-based decision making (based on Rangel, Camerer, & Montague, 2008, Figure 1).

According to this framework, each decision-making process begins with computing a representation of the choice problem (*state representation*). This includes all internal (e.g. hunger, thirst, boredom) and external variables (e.g. temperature, threat, surroundings) comprising the current state and, in addition, all imaginable actions in this state. This first process is neither well investigated nor understood regarding its computational and neurobiological foundations and many questions about it await answering, for example, how actions get chosen to be represented or ignored and how the necessary interplay between perception and memory retrieval works (Rangel et al., 2008).

Whatever the mechanisms behind this first process, the agent then computes a value for each option based on this state representation (*option valuation*). This is the process of most interest in current lines of research. Note that the computed values in this step refer not to the incentive value of the expected outcome but to the choice option itself, that is, a state-action pair. As there are several modulating features of options, for example the delay until receipt of the outcome and the current motivational state of the agent, the option value does not have to correspond to the incentive value of the respective outcome. For example, the same piece of pie has a certain relatively stable incentive value for the same agent, but the option to buy it can be valued very differently depending on whether one is hungry or sated, rich or poor, on

diet or underweight. In this second step of the VBDM process, one can differentiate at least three different valuation systems, being Pavlovian, habitual, and goal-directed. The Pavlovian system is based on "pre-wired", innate, archaic responses to specific stimuli like approaching appetitive (e.g. food) and withdrawing from aversive stimuli (e.g. predators). Thus, the behavioral repertoire of the Pavlovian system is very limited (Rangel et al., 2008). In contrast to the innate responses of the Pavlovian system, the habitual system has learned the values of stimulus-response associations through operant or instrumental conditioning, that is, through trial-and-error learning, the comparison of expected and received outcomes, and the consequent repetition of reinforced behavior (Daw, Niv, & Dayan, 2005). In consequence, state-action pairs that have often led to a rewarding experience are attributed with a relatively high value in the habitual system. These "habit values" need many experiential repetitions to approximate the real-world long-term values of stimulus-response associations, above all with complex behaviors, but once learned they can be retrieved directly. This immediacy of the value allocation is the greatest advantage of the habit valuation system. Unfortunately, the habit system can only assign values to previously experienced options and relies on generalization from known stimulus-response pairs when encountering new states (Rangel et al., 2008). This can lead to failures in value allocation and, hence, in behavioral control when an option is incorrectly valued and consequently erroneously chosen. The third proposed system in the option valuation process, the goal-directed system, is based on a model of the state space, that is, a map-like representation of the world with all thinkable actions transiting the agent from the current state to the next ones. This system computes values by forward planning, mental simulation, and calculating beneficial action trajectories through the state space with its knowledge of action-outcome contingencies, transition probabilities between states, and incentive values of outcomes. These "goal values" are computed on demand and can flexibly adapt to all features of the state representation (not only the previously encountered like the habit system's values), but their calculation is computationally expensive, effortful, and time-demanding (Daw et al., 2005; Gershman & Daw, 2017).

Furthermore, there are some known attributes in the state representation modulating the processes of the valuation systems. Risk, uncertainty, ambiguity, and delay of option outcomes, and social contexts can influence the valuation processes that are the basis for action selection. These influences are best understood within the goal-directed system as this can be examined in humans easiest, while it is still unclear whether and how these situational facets relate to Pavlovian and habit valuation (Rangel et al., 2008). In the context of risk and delay, the assumptions of Prospect Theory (Kahneman & Tversky, 1979) have often been

confirmed. This theory states that delays diminish the value of outcomes hyperbolically as does a probabilistic compared to a definitive receipt of rewards (see section 1.2.3.4 and Chapter 4/Study 3). Furthermore, Prospect Theory proposes that the valence has an influence on valuation processes. Thus, negative-valence outcomes are weighed stronger than positive-valence outcomes of the same absolute value (termed loss aversion, see section 1.2.3.4 and Chapter 4/Study 3).

The allocated values of this second process are then passed on to the next process and are the basis for the selection and execution of one action (*action selection*). How exactly the values of various options are integrated to select one for execution is still under investigation. Daw, Niv, and Dayan (2005) suggested the selection to be based on the relative certainty of the underlying valuation systems, which has found some empirical consolidation (Lee, Shimojo, & O'Doherty, 2014). Another approach is to build a weighted sum of the different values from the valuation systems for the same options and feed this into a function that also takes into account human's tendency to perseverate under some circumstances (e.g. exploitation behavior in stable environments) and to seek out novel options under other condition (e.g. exploration behavior in unstable environments; e.g. J. D. Cohen, McClure, & Yu, 2007; Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006). So far, many aspects of action selection have not been investigated, yet, like how this process handles conflict between values for the same option from different valuation systems, whether there is a hierarchy of the different systems, and how the selection process is implemented in the brain (Rangel et al., 2008).

After execution of the chosen action, the outcome of this action is being evaluated regarding its desirability or actually perceived incentive value (*outcome evaluation*). This evaluation is used to update the first three processes (*learning*) to improve behavior when facing the same or similar states in the future. The learning process has been suggested to involve reinforcement learning, that is, updating state values by the perceived outcome of an action, thereby increasing the probability of selecting actions that led to positive experiences in the past and decreasing the probability of choosing options with aversive consequences (see section 1.2.3.2).

Failures could theoretically arise in each of the VBDM processes and be associated with disorders of decision making like AUD, but most research so far focused on the valuation process (Rangel et al., 2008; Redish, 2004). Hence, the valuation systems might go wrong in assigning values for actions regarding alcohol use. Oftentimes, it is assumed that the habit system consistently overvalues choice options involving alcohol consumption in AUD, but it

is also possible for the goal-directed valuation system to underestimate the long-term harms of consumption and, thus, compute a subjectively heightened value for drinking (e.g. Redish, 2004). If the option values to consume alcohol are subjectively increased, the chance to choose this course of action is also elevated (as it is a general assumption underlying human behavior control theories that we choose the option with the highest subjective value most of the time). However, it is also possible that certain options are systematically ignored and not even represented as possible action trajectories at the beginning of the VBDM process. For example, it could just not occur to a person suffering from AUD to pour away an opened bottle of liquor or to not attend a family birthday party, where the temptation to drink might be high. In addition, the action-selection process might be corrupted in AUD systematically selecting the alcohol-associated option when the values of the option to drink and the option to abstain are in conflict but equally high.

Still, the valuation process of VBDM is the best understood and especially the interplay between goal-directed and habitual valuation systems has been of great interest for research on decision-making processes in general. In the last 20 years, the idea of those two opposing systems was adopted to clinical research and sparked investigations into their possible role in the development and maintenance of several mental disorders. However, as Rangel, Camerer, and Montague (2008) have put it, the five proposed processes of VBDM are not rigid. Their model is just one possible taxonomy trying to organize the decision-making process and, thus, aid in structuring and linking research from neuroeconomics, psychology, psychiatry, and cognitive neuroscience. This is important to keep in mind when revisiting literature on this topic as many researchers did not restrict goal-directed and habitual systems to the process of option valuation like proposed by Rangel, Camerer, and Montague (2008). Instead, they often assumed these two systems to each comprise separate state representations, valuation and updating rules, and to compete with one another for supremacy in action control. Until today, there is no consensus in the scientific community about how many decision-making systems exist and how the various sub-processes are implemented and interact despite a tremendous amount of research on this topic as I will outline in the following section. Solving these issues will be an important avenue of future research and some computational approaches used in the more recent investigations hold promise to bring us closer to a better understanding of the interplay of goal-directed and habitual systems involved in VBDM.

1.2.3 Goal-directed and habitual systems

The dual-system account of a flexible, executive or cognitive system opposed to an automatic habitual one put forward by Redish, Jensen, and Johnson (2008) has a long history in psychology with a strong focus on animal models of behavior until the end of the last century. Even theories as old as Tolman's (1948) cognitive maps in rat navigation research can be re-interpreted with this framework: rats put in a maze learned a comprehensive map of the maze and were able to flexibly adjust their behavior when paths were changed or the whole maze rotated except for the food box and some global orientation cues in the room, where the maze had been set up. But with overtraining or too strong motivational or frustrating states (e.g. by being very hungry during training), the cognitive maps supposedly narrowed down and became "strip-like" often only storing a single, simple path to the goal (Tolman, 1948). This description bears strong resemblance to an elaborated, cognitive, goal-directed system building a map of the world one lives in becoming a habitual stimulus-response or state-action sequence after many repetitions seen in later rodent and human experiments of behavioral control (e.g. Adams, 1982; Dickinson, 1985; Tricomi, Balleine, & O'Doherty, 2009).

Based on experimental and theoretical work in rodent models of learning and behavioral control, Dickinson (1985) described a system being more reflexive and based on stimulus-response patterns and another ("teleological") system that plans action in a purposeful, goal-directed manner. Nine years later, Dickinson and Balleine (1994) proposed two criteria for the definition of goal-directed behavior: (i) the *instrumental criterion*, that is, a goal-directed action has to be mediated by the representation of the contingency between action and outcome and (ii) the *goal criterion*, that is, the outcome has to have an incentive value for the agent and, therefore, poses a desirable goal state. These criteria imply that an agent needs instrumental learning to memorize the contingencies between actions and outcomes on the one hand and incentive learning to estimate the value of an outcome on the other.

Instrumental learning has been an area under research for a century starting with pioneer work by Thorndike (1911) and many more (e.g. Grindley, 1932; Miller & Konorski, 1969; Skinner, 1938). It is defined by the necessity of an action or response to receive an outcome (Koch, 2008). In the first instantiations of instrumental learning by Thorndike, the outcome was assumed to reinforce the stimulus-response association that led to its receipt but was not itself a part of the learned entity. Furthermore, all learned instrumental behavior was assumed to be elicited by external stimuli. But Skinner (1938) opposed this view. He defined another class of instrumental behavior called operant behavior besides these stimulus-response

associations (which he called respondent behavior). Operant behavior is instrumental in earning an outcome but not elicited by an external stimulus. Here, one can see the first differentiation between two ways of behavioral control: externally triggered stimulus-response patterns and behavior guided by internal action-outcome associations reminiscent of modern accounts of habitual and goal-directed control, respectively.

Incentive learning is the answer to the question, why some entities can pose a desired goal for an individual. Tolman (1949) called this cathexis – the connection of a positive or negative goal object to a positive or negative drive, respectively. If a hungry being, for example, faces and consumes a certain type of delicious food for the first time, it will immediately associate this food type with a pleasurable reduction of hunger. Thereby, this type of food has acquired positive incentive value for the creature. The process of incentive learning is an essential prerequisite of instrumental learning as it provides valuable reinforcers of behavior. But it is also crucial for one of the two classic animal experiments demonstrating goal-directed behavior, devaluation paradigms.

In outcome devaluation experiments, an agent learns a stimulus-response-outcome association. After learning, the outcome is devalued either through satiation or by new, this time negative, incentive learning. In the latter case, the valued outcome is paired with a strong unpleasant experience, for example an injection of lithium chloride resulting in acute malaise, and, thereby, the agent experiences a great decrease in incentive value of this outcome. The other classic paradigm for the demonstration of goal-directed behavior is contingency degradation, where the contingency between action and outcome is being manipulated after learning, for example by giving non-contingent doses of the outcome. Both paradigms include testing the instrumental behavior rates of animals after these manipulations. The final test of response rates is conducted in extinction, because supposedly no new learning occurs when holding back the outcome (or response rates just slowly decrease over time depending on the previous stability of learned behavior). Seeing a strong decrease in instrumental responding after outcome devaluation or contingency degradation is a sign that this behavior was characterized by the goal and instrumental criterion and, thus, goal-directed by definition.

Studies employing contingency degradation or outcome devaluation have also revealed that instrumental behavior can get impervious to these manipulations under certain circumstances. Extensive training is one of these circumstances (e.g. in rats: Adams, 1982; Dickinson, 1985; in humans: Tricomi et al., 2009). Over-training is supposed to lead to a representational dissociation of the stimulus-response association from the outcome value, that is, behavior is executed in the form of automatic responses to external stimuli

independent from the current value of the outcome of this response. Behavior that is governed this way is called habitual. In other words, numerous repetitions of the same behavior lead to a shift from initially goal-directed to habitual control. This shift is the heart piece of a current theory on the development of SUDs (Everitt & Robbins, 2016).

1.2.3.1 Goal-directed and habitual decision making in association to alcohol dependence

Everitt and Robbins (2005, 2013, 2016; Robbins & Everitt, 1999) proposed a learning-based theory of the development and maintenance of and relapse to SUDs. In their account, drug consumption is an intentional and goal-directed process at first. After repeated drug intake, the consumption pattern can gradually shift from goal-directed to habitual control. This idea of a transitional process of first voluntary, controlled to later automatic behavior in alcohol (ab-)use was partly based on a review by Tiffany who stated that drug usage becomes an automatic "drug-use action plan" through "consistent practice" (Tiffany, 1990; pp. 154-155). The transition is supposed to be facilitated by the sustained reinforcing effects of drugs of abuse, which are probably mediated by dopaminergically innervated cortico-striatal loops (see section 1.3).

The learning theory account of addiction by Everitt and Robbins is mostly based on rodent studies examining effects of outcome devaluation and contingency degradation and gave rise to extended research. Following their claim, researchers showed that using drugs of abuse as rewards in repeated instrumental learning scenarios led to resistance against outcome devaluation more rapidly or stronger than using natural rewards like food or sugar water (e.g. Clemens, Castino, Cornish, Goodchild, & Holmes, 2014; Corbit, Nie, & Janak, 2012; Dickinson, Wood, & Smith, 2002; Miles, Everitt, & Dickinson, 2003; Nordquist et al., 2007). Furthermore, it has been shown that alcohol and amphetamines facilitate habitual responding instead of goal-directed behavior towards natural rewards even when given before and independent from the instrumental task (Corbit et al., 2012; Nelson & Killcross, 2006). This was interpreted as drugs' general ability to enhance the transition of behavioral control from goal-directed to habitual regardless of the type of reinforcer. Yet, this rich line of animal research has focused strongly on reward-seeking behavior and not examined habitual drug intake specifically (McKim, Shnitko, Robinson, & Boettiger, 2016). Though Everitt and Robbins' learning theory of addiction assumes the same mechanisms to be at work in human beings suffering from SUDs, empirical investigations with human subjects remain sparse.

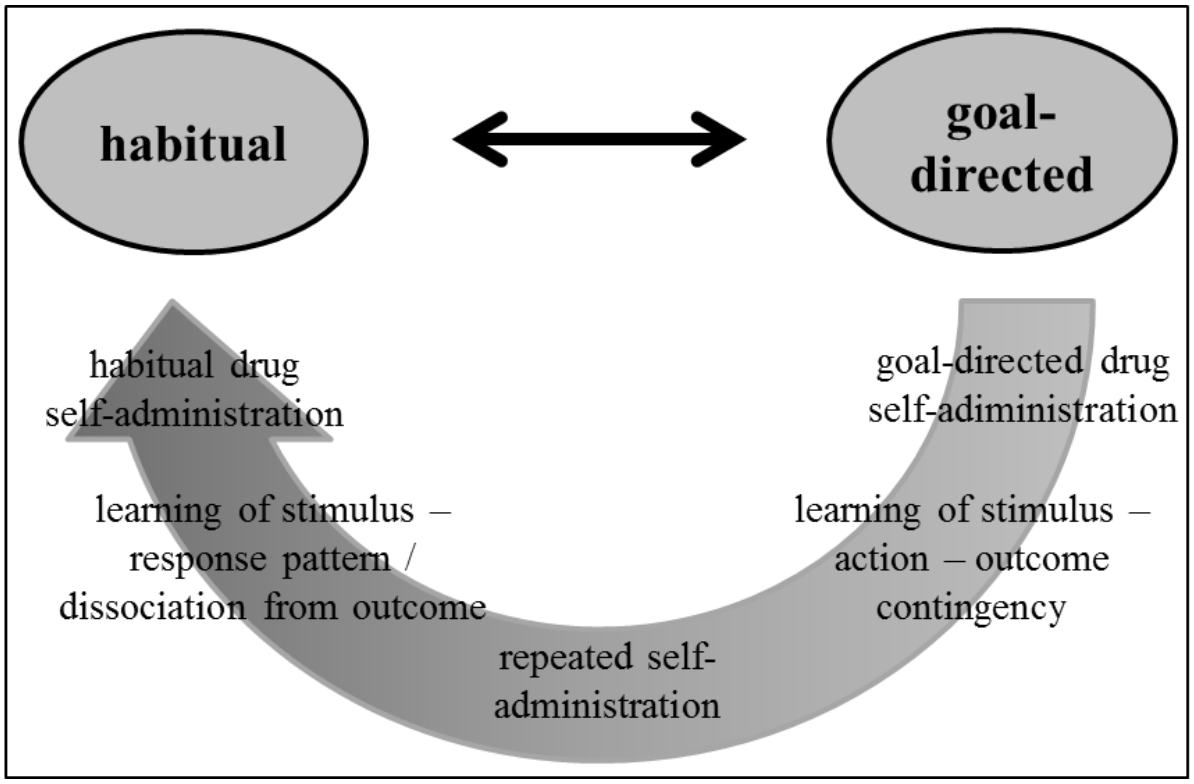

Figure 2 Schematic representation of the shift from initially goal-directed substance us to automatic, habitual drug intake (based on Everitt & Robbins, 2016).

Sjoerds et al. (2013) examined the effect of outcome devaluation in a slips-of-action task (S. de Wit, Corlett, Aitken, Dickinson, & Fletcher, 2009; S. de Wit, Niry, Wariyar, Aitken, & Dickinson, 2007) in detoxified AUD patients compared to healthy control participants. They found decreased accuracy in AUD patients after devaluation for all trial types, where the assumption of a shift from goal-directed to habitual control would have predicted specific deficits in two out of three trial types. This is in line with findings of rodent experiments by Halbout, Liu, and Ostlund (2016) showing that the previously shown shift to habitual responding was not apparent anymore when they used a more complex behavioral task than the studies before. These findings may weaken the evidence for the proposed model by Everitt and Robbins (2005, 2016), at least for AUD, but cannot refute it. Yet, they indicate that the relationship between alcohol consumption and behavioral control may be more complicated than can be examined with classic devaluation or degradation tasks – especially in human beings. Though, we do not know this for certain, yet, as a study like the one by Sjoerds et al. (2013) has not been repeated to date.

1.2.3.2 Model-free and model-based reinforcement learning

Instead of trying to translate the investigation with devaluation and degradation paradigms in animal models to the human domain (Sjoerds et al., 2013), some SUD researchers turned towards another class of experimental paradigms. This shift of paradigm also addressed a fundamental shortcoming of devaluation and degradation tasks. Behavior that did not fulfill the instrumental and goal criterion of goal-directed behavior was assumed to be habitual by default. This accounts for the previously mentioned experiments not leaving room for alternative interpretations: response rates were either susceptible to the decrement of outcome value or contingency between response and outcome, that is goal-directed, or they were not and, thus, habitual. But there were no experimental paradigms to examine a possible "middle way" between or interaction of these systems. This changed when research on goal-directed and habitual control was brought together with reinforcement learning (RL) models from computational learning theories.

Reinforcement learning systems comprise four key elements: a policy, a reward signal, a value function, and (optionally) a model of the environment (Sutton & Barto, 1998). A *policy* maps or stores the preference to execute certain actions in certain states. The *reward signal* can be imagined as a single number that represents the amount or magnitude of reinforcing outcome an agent has received in each time step. This information is used to compute a *value function*, which represents the desirability of reaching a certain state and acting on a certain policy from this state onwards. While the reward signal stands for the immediate reinforcement after reaching a state, the value function estimates the prospective, cumulative reinforcement in this state and the possibly following states. Last, the *model* (or so-called state space) comprises a tree- or net-like map of the current and all possible future states including the possible transitions between states via certain actions.

In the RL literature, two modes of learning have been established: model-free and model-based RL (e.g. Dickinson & Balleine, 2002; Doya, 1999; O'Doherty, Cockburn, & Pauli, 2017). Daw, Niv, and Dayan (2005) suggested that model-free and model-based RL algorithms could be used to model habitual and goal-directed decision-making systems, respectively, as they share pivotal properties. Model-free RL (Barto, Sutton, & Anderson, 1983; Rummery & Niranjan, 1994; Sutton & Barto, 1998) learns by trial-and-error and uses reward prediction errors (RPEs) as teaching signals in order to update cached values of stimulus-response associations – or, in terms of RL, state-action pairs. RPEs arise from a comparison of expected and actually received outcomes after executing an action. Because of this updating scheme, model-free RL is only dependent on the previous reward history in this

specific state and, therefore, an ideal operationalization of habitual control. State-action pairs that have led to reward more often are more likely to be repeated, reminiscent of Thorndike's (1911) Law of Effect. Model-based RL, on the contrary, works by building a map of the state space. It also integrates values for states according to the expected reward in that state and the sum of all possible future rewards (which might be learned by model-free RL; Daw, Gershman, Seymour, Dayan, & Dolan, 2011). A model-based RL agent then searches its model of the state space for the most beneficial trajectory through it and executes the resultant policy. This dependence on a cognitive model of the world is strongly akin to the way the goal-directed system controls behavior.

The basis for most RL models is Bellman's equation (Bellman, 1957; cf. Gershman & Daw, 2017), which defines the value of a state-action pair ($Q_\pi(s_t, a_t)$) as the reward (r_t) received by that action (a_t) plus the time-discounted sum of all the possible following states ($Q_\pi(s_{t+1}|\pi(s_{t+1}))$ weighted by the probability of reaching them ($P(s_{t+1}|s_t, a_t)$). In this equation, *t* denotes the current time step, *s* a state, *a* an action, γ the time-discounting parameter, *Q* the value for a state-action pair, *P* a probability, and π a policy.

$$[1] \qquad Q_\pi(s_t, a_t) = r_t + \gamma \sum_{s_{t+1}} P(s_{t+1}|s_t, a_t)\, Q_\pi(s_{t+1}|\pi(s_{t+1}))$$

The concept of time discounting is not crucial for understanding here and will be introduced in section 1.2.3.4. Model-free and model-based RL can be seen as two different approaches to solve Bellman's equation (Gershman & Daw, 2017). As model-based RL comprises a model of the state space and the associated rewards, it can calculate the right-hand side of Bellman's equation by planning of future trajectories, thereby trying to find the optimal policy maximizing future rewards. In contrast, model-free RL tries to estimate the left-hand side of the equation directly by past experience and stores the estimate in a memory cache to be updated each time the agent visits this state-action pair. The instantiation of model-free RL used in the presented studies was the so-called state-action-reward-state-action (SARSA) temporal difference (TD) learning algorithm proposed by Niranjan and Rummery (1994; see Appendix A.1.1). This recursive algorithm updates the current estimate of the state-action pair ($Q_{TD}(s_t, a_t)$) by the RPE (δ_t) that is weighted by a learning rate (α).

$$[2] \qquad Q_{TD}(s_t, a_t) = Q_{TD}(s_t, a_t) + \alpha\delta_t$$

As mentioned previously, the RPE represents the comparison between the expected reward (i.e. the value of the state-action pair after its last encounter; $Q_{TD}(s_t, a_t)$) with the actually received reward (r_t) and the time-discounted (γ) value of the next state-action pair ($Q_{TD}(s_{t+1}, a_{t+1})$).

[3] $$\delta_t = r_t + \gamma\, Q_{TD}(s_{t+1}, a_{t+1}) - Q_{TD}(s_t, a_t)$$

When having experienced this state often enough (given that the environment and its reward structure are stable), the expected reward equals the sum of received reward and time-discounted future-state value function and, thus, the RPE is zero. If the RPE is non-zero, the estimated value function of this state-action pair is updated. In contrast to these approximations of state-action values by the model-free system, the model-based RL system is assumed to directly build a model of the state space and uses this model to prospectively plan the most beneficial path through the tree-like model.

Daw et al. (2011) designed a task that can model the balance between model-free and model-based RL (called the Two-Step task; see Figure 3). This sequential decision paradigm includes a probabilistic transition structure between states in each trial. Model-free and model-based RL state-action values can be differentiated, because the model-free system is oblivious of the transition probabilities and, therefore, ascribes a change of value to the wrong option under specific circumstances. Daw and colleagues also conceived a computational model of task behavior, which can be fit to the choices of each individual. This computational model uses the aforementioned equations for the model-free option values, calculates model-based values by combining these model-free values with the transition probabilities between states (see Appendix A.1.1), and also combines both model-free and model-based option values to a net value of each state-action pair. In the combination, both types of option values are weighted by the parameter ω ranging from completely model-free (ω=0) to completely model-based (ω=1). This way of combining option values implies that model-free and model-based valuation are the end points of one continuum and that behavioral control is commonly based on the integration of both modes of valuation. Crucially, this computational modeling approach outputs one parameter estimate of ω for each subject, thereby approximating the individual set point of the balance between model-free and model-based valuation modes in performing this task. This allows the examination of interindividual differences in this balance and their association with third variables like measures of alcohol consumption.

1.2.3.3 Model-free and model-based reinforcement learning in association to alcohol use

As mentioned previously, some addiction research groups turned to this reinforcement-learning paradigm to overcome the shortcomings of devaluation and degradation paradigms and to examine the relationship between alcohol use and the balance between model-free and model-based RL. Model-free and model-based RL are suggested to be proxies for habitual and goal-directed control, respectively, with the aim to examine the claim of Everitt and Robbins (2016) that AUD is associated with a shift from goal-directed to habitual control. Using Daw's Two-Step task (Daw et al., 2011), these studies yielded mixed findings. With data of our pilot study, we compared AUD patients in detoxification with control participants matched for age and sex (Sebold et al., 2014). We found a decrement of model-based control in AUD patients, which disappeared after controlling for group differences in cognitive speed. In contrast, Voon et al. (2014) did not find differences in the balance between model-free and model-based control between AUD patients and healthy control subjects, but they did find a correlation between ω and the number of weeks abstinent in the patients with longer abstinence being associated with stronger model-based control. This correlation could explain the discrepancy to our finding in the pilot study (Sebold et al., 2014). AUD patients in Voon's study were abstinent for two weeks to one year, while our pilot patients have been abstinent for two to 39 days. This could indicate that patients in Voon's study were more model-based and, thus, more similar to healthy controls on average. Gillan et al. (2016) used a different approach sampling data from 1,413 subjects of the general population via an online assessment. They reported a small negative association between the degree of model-based control and self-reported alcohol use. Another study by Reiter et al. (2016) using the Two-Step task found no difference in the balance between model-free and model-based control comparing healthy participants with and without family history of alcohol dependence.

Overall, the current state of research is ambiguous about the association of alcohol use with goal-directed and habitual control in human subjects. There is no clear evidence for the proposed shift from goal-directed to habitual control during the development and maintenance of an AUD, but this theory could also not be clearly refuted, yet. It is possible that this shift only occurs in especially severe cases of AUD, develops after a long period of chronic alcohol abuse, or does not generalize to control in non-drug related behavior. Moreover, a general bias towards habitual behavior in AUD, if it exists, or a tendency to faster progress from goal-directed to habitual control could also pose premorbid vulnerability factors for out-of-control alcohol use. It is one aim of this thesis to further elucidate this relationship (Studies 1 and 2).

Another important issue in investigating the association between VBDM and alcohol use is the aforementioned influence of features of the options like the delay between action and outcome or the uncertainty of the outcome (e.g. Rangel et al., 2008; Redish et al., 2008). These features have been shown to modulate the valuation of options (Kahneman & Tversky, 1979) and this modulation shows interindividual differences and relative intraindividual stability (Green & Myerson, 2013). This gives rise to the question whether associations of alcohol use and VBDM are really driven by general tendencies to utilize more goal-directed or habitual control or by how the individual weights these modulating features. For example, a high subjective value for drinking alcohol in the current situation might be derived from a habitual bias of this valuation system towards alcohol as a direct consequence of many previous rewarding encounters with alcohol. Alternatively, this increased value could result from the discounting of negative long-term consequences of alcohol use, which in turn leads to an increased goal value of drinking. Thus, the individual weighting patterns of these specific option features might prove as important for the development and maintenance of AUD as the broader concepts of option valuation in VBDM.

1.2.3.4 Modulators of goal-directed and habitual valuation systems

As described previously, numerous features of the current options have to be taken into account during the valuation process in VBDM. These features include among other things the probability or uncertainty of the outcome, the delay until its receipt, the social context during decision making, and the effort to be exerted to gain the outcome. All those characteristics of the options modulate the valuation processes in the Pavlovian, habitual, and goal-directed system. How this modulation works is mostly not well understood, especially for the Pavlovian and habitual system, but some modulators have received more attention in research than others (Rangel et al., 2008), especially those which adhered to an impulsive phenotype often encountered while working in clinical settings. This phenotype showed certain general biases in weighting these modulating features termed impulsive choice tendencies (Green & Myerson, 2013).

Impulsivity is a very broad multi-faceted construct that is either representing "a failure to process information sufficiently or to control response output" (Dalley & Robbins, 2017, p. 158). Wilcox et al. (2014) give an incomplete list of constructs or facets that had been put under the umbrella term impulsivity: "responding before instructions are given or completed, responding without considering all options, inability to refrain from responding to an inappropriate stimulus, acting without considering the full set of consequences and without

forethought or planning, risky decision making/risk taking, urgency (both positive and negative), impatience, carelessness, difficulty paying attention, novelty seeking, pleasure seeking, greater reward sensitivity, an underestimated sense of harm, lack of perseverance, impairments in time estimation, impairments in learning from negative consequences or punishment, and extroversion […] overvaluing short-term rewards and undervaluing greater long-term rewards, showing impairments in delaying gratification, and delay discounting" (Wilcox et al., 2014, pp. 2–3). There were several attempts to structure impulsivity's subcomponents. One of them divided impulsivity into two areas: impulsive action and impulsive choice (Dalley & Robbins, 2017; Dalley & Roiser, 2012; Reynolds, Ortengren, Richards, & de Wit, 2006; Winstanley, Olausson, Taylor, & Jentsch, 2010). Impulsive action refers to behavior associated with decreased motor inhibition, whereas impulsive choice relates to decision-making tendencies based on biased evaluation processes. Impulsive choices often seem myopic, irrational, or just not properly thought through. Oftentimes, choice impulsivity is being operationalized by discounting processes as these can be easily studied and seem to be a part of many real-life decisions.

One of the modulating features of options, which have been investigated extensively, is the delay until the receipt of an outcome. In general, agents show a tendency to discount delayed rewards not linearly with increasing delay but hyperbolically or hyperbola-like (Green & Myerson, 2004, 2013). Thus, they tend to prefer sooner smaller (e.g. 10 € immediately) over larger later rewards (e.g. 20 € received in four weeks). An impulsive choice tendency in delay discounting is marked by overweighting delays and being rather impatient/unable to wait for gratification and, therefore, higher discounting (Green & Myerson, 2013).

Furthermore, the valence of options has an influence on choice behavior. This addresses the asymmetry in the valuation of rewards and punishments, that is, punishments or losses are not just being processed and weighted as inversed or negative rewards. Quite the opposite, punishments are often more salient and their absolute subjective value is commonly higher than that of a gain of the objectively same absolute value (Kahneman & Tversky, 1979) making most humans on average rather loss averse. Hence, most human beings would not take a bet where they could either win or lose 10€ with a chance of 50% each. Instead, a gain in such a 50/50 gamble would have to be of a significantly higher value than the loss (Kahneman & Tversky, 1979; Tom, Fox, Trepel, & Poldrack, 2007). Like risk aversion, individual loss aversion is supposed to be rather stable but can be modified by acute

motivational states. Moreover, Ernst et al. (2014) have suggested that low loss aversion might be related to impulsivity.

Another rather well-described modulating feature in the valuation process is the stochasticity of outcomes. Most decision problems entail the chance that the agent does not receive the anticipated or desired quality or quantity of the outcome. Commonly, the riskiness of an outcome reduces the subjective value of it stronger than would rationally be expected. Thus, the subjective value of receiving 100 € with a 40% probability would not equal 40 € for most persons but be reduced to an even lower value. This decrement of subjective value is called discounting. The general population has been shown to discount the value of probabilistic gains preferring smaller certain over larger uncertain rewards (e.g. preferring 40 € for sure over 100 € with a probability of 40%) and, thus, be rather risk averse in the gain domain (Kahneman & Tversky, 1979). Showing less risk aversion than the general population, that is, underweighting risks and being rather risk-taking is deemed to be impulsive (Green & Myerson, 2013).

Discounting of risky and delayed rewards has been addressed in one of Redish, Jensen, and Johnson's (2008) vulnerabilities in the UFA, because research over the past decades had shown stable differences in discounting rates between patients suffering from SUDs and healthy comparison subjects. According to this line of research, SUD patients tend to show stronger discounting and, therefore, "overemphasize near-term rewards and underemphasize far-future costs" (Redish et al., 2008; p. 425), are more risk taking and impatient. On a broader scale, SUD patients have been shown to be more impulsive in several facets of impulsivity but the nature of the relationship between impulsivity and SUDs is still unclear (Dalley & Robbins, 2017; Winstanley et al., 2010). Impulsive choice tendencies might be a predisposing factor for the development of SUDs, but it may also result from prolonged substance use. Therefore, longitudinal and intervention approaches are needed to establish a model of causal relationships. Additionally, a big part of the previous research has investigated other substances than alcohol and assumed that the alterations would be equivalent over different substance classes. Although there have been attempts to validate this claim (see meta-analysis of delay discounting and various SUDs by MacKillop et al., 2011), further investigation into similarities and differences between modulators and substances is needed.

In summary, there are several valuation and behavioral control systems supposed to be at work in decision-making in general, which might be altered in AUD. The differentiation between goal-directed and habitual control systems has delivered many valuable insights in

this regard in rodent models, but so far translational research in humans is sparse and inconclusive. Heretofore, the literature gives no clear account on whether goal-directed control is indeed diminished in AUD in favor of habitual strategies, how known modulating features of option valuation (i.e. delay, risk, and valence) are altered in AUD, and whether these possible changes may also precede the onset of AUD to pose a risk factor for its development.

1.3 Neurobiological perspectives on alcohol use disorders

Pathological alcohol use has causes and consequences on many levels besides the ones in VBDM reviewed in the previous section. The mechanisms in this psychological domain are also complemented, caused, or followed by various processes on a genetic, epigenetic, synaptic, neuronal, glial, and neural circuitry level. As describing all the previously studied neurobiological facets would exceed the scope of this thesis, I refer the interested reader to the review by Volkow and Baler (2014) who give an elaborated overview of addiction seen as a neurobiologically complex disorder. I will first focus on general reward processing related neural mechanisms as these are crucial to understand the neural underpinnings of VBDM (for extensive and excellent reviews about the neural underpinnings of reward processing and learning, see Haber & Behrens, 2014; Haber & Knutson, 2010; O'Doherty et al., 2017). Then, I will introduce the neural mechanisms underlying goal-directed and habitual systems and, finally, how the brain adapts to chronic alcohol use.

1.3.1 Neural underpinnings of the reward circuit

Processing of reward information takes place in a vast neural network comprising cortical and subcortical areas. Research in the past decades suggested that there is a loop structure underlying the reward circuit (Haber, 2016; Haber & Knutson, 2010). At the heart of this circuit are two midbrain regions containing dopaminergic neurons, the ventral tegmental area (VTA) and substantia nigra (SN). Research has shown that rewards elicit a short-latency burst of activation of certain neuron populations in SN and VTA (Schultz, 1986) which decreases proportional to the increase of the probability or "expectedness" of the reward until it is reduced to the mere baseline firing rate in completely expected rewards (Fiorillo, 2003). Interestingly, this phasic activation of dopaminergic midbrain neurons is depressed below the baseline firing rate at times when an expected reward fails to appear (Schultz, Dayan, & Montague, 1997). This result pattern from studies working with electrophysiological

recordings from monkey midbrain structures corresponds to the characteristics of RPEs. These learning signals driving model-free RL are reduced to zero when received rewards were completely expected, positive at surprising deliverance of rewards, and negative when expected rewards fail to appear.

The reward information encoded in the activation patterns of dopaminergic midbrain neurons is then conveyed through afferent projections to the striatum. Here, the dopaminergic output from SN and VTA modulates the excitation of striatal neurons (Surmeier, Ding, Day, Wang, & Shen, 2007). Crucially, the connection between midbrain nuclei and striatum is not unidirectional. The striatum sends back projections to SN and VTA building a feed-forward loop structure. The nodes in these loops progress from medial to lateral parts of the midbrain and from ventromedial to dorsolateral regions of the striatum with each iteration (Haber & Knutson, 2010).

The areas within the striatum do not only receive input from and send projections to midbrain nuclei, but are also convergence zones of the projections from several other brain areas (Haber & Behrens, 2014; Haber, Kim, Mailly, & Calzavara, 2006; Haber & Knutson, 2010). This allows for information encoded in other brain regions to be integrated and incorporated into the reward-processing circuit. As far as we know, most important for this is the ventral striatum, a structure loosely defined as comprising nucleus accumbens (NAcc), ventromedial caudate, and rostroventral putamen (Haber & Knutson, 2010). In the ventral striatum, there are convergence zones of projections from orbitofrontal cortex (OFC), dorsal anterior cingulate cortex (dACC), and ventromedial prefrontal cortex (vmPFC). These three regions have often been implied to encode different aspects of anticipating, processing, and evaluating rewarding and punishing outcomes. The complex patterns of convergence in ventral striatum provide a possible anatomical substrate of integrating the different facets of reward information represented in the activation of those areas (Haber & Behrens, 2014; Haber et al., 2006; Haber & Knutson, 2010; Yin, Ostlund, & Balleine, 2008).

Different OFC cell populations encode different features of an option, like the size, probability, and cost of an outcome (Haber & Knutson, 2010; Schoenbaum & Roesch, 2005) which makes the OFC a candidate area underlying the modulation of option valuation by these features. OFC receives both primary and highly processed sensory information input as well as connections from amygdala and the ACC (Haber & Behrens, 2014). Classic experimental tests of OFC functionality are reward devaluation and reversal learning tasks as agents with lesions to the OFC display difficulties in adapting previously learned associations to new value information. This has been accredited to OFC's role in using perceptual

information about presented stimuli to evoke sensory representations of the outcome, which in turn can be evaluated and drive learning (Burke, Franz, Miller, & Schoenbaum, 2008; Haber & Behrens, 2014). As this deficit after OFC lesions is based on the coupling of sensory information of stimuli and outcomes, it disappears when actions instead of pure perceptual stimuli are associated with the outcomes (Haber & Behrens, 2014).

While different features of an option are encoded by different OFC cell populations, there is one population of dACC cells coding for an integrated value signal combining all the properties of it, that is, dACC activation entails integrated action values in units independent from actual actions and outcomes (Haber & Behrens, 2014). Cell populations within dACC are also able to relate these action values to the cost of that action at decision points and, thereby, controlling the balance between exploration and exploitation (Haber & Behrens, 2014).

The caudal part of the vmPFC has strong connections to hypothalamus, amygdala, and ventral striatum, whereas the rostral part has connections mostly to the frontal pole, dorsolateral (dlPFC) and dorsomedial prefrontal cortex (dmPFC; Haber & Behrens, 2014). Together, the vmPFC areas can compute and encode values of options, especially in the context of internal (motivational) states. This value computation can happen "on the fly", that is, directly at choice points and possibly independent from previous experience with the current options. Humans' ability to generalize from features of an option to similar but different options that have never been encountered before probably relies on this function of vmPFC, as well as the goal-directed valuation of current options. The ability of online value computations might be a unique feature of vmPFC in comparison to all other brain areas.

These three regions – OFC, dACC, and vmPFC – compose the main cortical input to the ventral striatum and their information is combined with the information from DA midbrain nuclei, amygdala, hippocampus, and insula there. As this enriched reward information is then spiraled from the ventral to the dorsal striatum, action plans are invoked and, finally, executed. Whether these different processes take place serially, in parallel or as a combination of both is still an open question (Haber & Behrens, 2014) though the abovementioned convergence zones strongly advocate for at least partially parallel processing.

VBDM entails processing of reward information at least in the option valuation and outcome evaluation stages, but most likely all processes in VBDM are associated with this vast reward-related network with a strong emphasis on ventral striatum, vmPFC and OFC. The next section will give an overview of our current knowledge about the neural implementation of goal-directed and habitual valuation and behavioral control.

1.3.2 Neural underpinning of goal-directed and habitual decision making

Numerous studies have examined the neural correlates of habitual and goal-directed control systems in the past decades, mostly working with animal models and the classical experimental paradigms of outcome devaluation and contingency degradation. Findings in this regard showed that the behavioral effect of outcome devaluation and contingency degradation in extinction was abolished after lesions of the dorsomedial striatum, which is the rodent equivalent of the (posterior) caudate, whereas lesions of the dorsolateral striatum, corresponding to human (posterior) putamen, prevented instrumental behavior to become habitual after extended training (Balleine & Dickinson, 1998; Goodman & Packard, 2016; Graybiel, 2008; Voon, Reiter, Sebold, & Groman, 2017; Yin, Knowlton, & Balleine, 2006, 2004; Yin, Ostlund, Knowlton, & Balleine, 2005; Yin & Knowlton, 2006; Zapata, Minney, & Shippenberg, 2010). In addition, lesions of NAcc shell did not result in changes of the sensitivity towards outcome values or contingencies and, hence, did not affect the performance of goal-directed or habitual responses, while lesions of NAcc core left sensitivity to contingency degradation intact but interfered with rats' sensitivity to outcome devaluation (Corbit, Muir, & Balleine, 2001; Yin et al., 2008). These dissociable effects of lesions to various striatal regions suggest that NAcc may be involved in the acquisition but not performance of goal-directed and habitual behavior, while there seems to be a focus of control of goal-directed behavior in caudate and of habitual behavior in putamen (Graybiel, 2008; Yin, Ostlund, & Balleine, 2008).

Furthermore, there is evidence for a shift of control from dorsomedial to dorsolateral striatum in rats and primates accompanying the behavioral shift from goal-directed to habitual control under certain circumstances, for example extended training (Haruno & Kawato, 2006; Tricomi et al., 2009; Yin et al., 2008). In addition to these findings regarding different areas of the striatum, there is empirical evidence for a role of prefrontal regions in goal-directed and habitual control. Findings here are less conclusive, but suggest a role of prelimbic cortex in goal-directed and infralimbic regions in habitual control (Balleine & Dickinson, 1998; Graybiel, 2008; Voon et al., 2017). Unfortunately, it is still unclear, what the human analogue regions to those rodent prefrontal areas are. It has been suggested that, based on the pattern of thalamic input to these regions, prelimbic rodent cortex corresponds to the pregenual ACC (Brodmann area 32) and infralimbic cortex to human subgenual ACC (Brodmann area 25; Gass & Chandler, 2013).

Translational neuroimaging research in humans corroborated findings from animal studies using equivalent paradigms. Valentin, Dickinson, and O'Doherty (2007) found

activation in OFC to encode option values during an outcome devaluation task using specific satiation that corresponded to the valuation scheme of a goal-directed controller. Tricomi, Balleine, and O'Doherty (2009) showed increasing task-related activation of posterior putamen with extended but not limited training in a similar devaluation task suggesting this area to be related to habitual control. Two more fMRI studies using the slips-of-action task (de Wit et al., 2007) have shown goal-directed behavioral control to be associated with increased activation in vmPFC (de Wit et al., 2009) and increased structural connectivity between caudate and vmPFC and decreased connectivity between posterior putamen and premotor cortex measured with diffusion tensor imaging (S. de Wit et al., 2012). Furthermore, Gläscher and colleagues could show that the model-based system relies on state representations being stored and updated in the intraparietal sulcus and dlPFC (Gläscher, Daw, Dayan, & O'Doherty, 2010). The cognitive map, which is based on these state representations and is assumed to underlie goal-directed control and model-based RL, seems to be represented in a network comprising the hippocampus, OFC, dlPFC, and posterior parietal cortex (O'Doherty, Cockburn, & Pauli, 2017). Moreover, Daw et al. (2011) showed blood-oxygen level-dependent (BOLD) responses in ventral striatum and vmPFC to be associated with model-free RPEs but to also comprise signatures of the model-based valuation system using the Two-Step task to investigate neural correlates of model-free and model-based reinforcement learning. In addition, model-based control in the Two-Step task has been shown to be modulated by various manipulations: application of L-DOPA to healthy volunteers, which enhances dopamine levels systemically, enhanced model-based control (Wunderlich, Smittenaar, & Dolan, 2012); disrupting right dlPFC activation via transcranial magnetic stimulation reduced model-based control in favor of model-free behavior (Smittenaar, FitzGerald, Romei, Wright, & Dolan, 2013), but anodal transcranial direct current stimulation of the same prefrontal area did not change model-free and model-based control (Smittenaar, Prichard, FitzGerald, Diedrichsen, & Dolan, 2014).

In summary, goal-directed behavioral control is assumed to be dependent on vmPFC and OFC in interaction with dorsomedial striatum (i.e. caudate; Everitt & Robbins, 2016), which fits well with OFC's role in representing various facets or features of options and vmPFC's role in the online integration of these to calculate subjective values (see section 1.3.1). Caudate also integrates information from hippocampus, ACC, intraparietal sulcus, and dlPFC, which could give rise to the representation of the mental map of the state space goal-directed control is based upon. In contrast, habitual behavior seems to be based on dorsolateral striatum (i.e. putamen) and possibly (pre-)motor cortical areas (Balleine &

O'Doherty, 2010; Everitt & Robbins, 2016; Yin et al., 2004). These findings map well onto the reward-processing circuits, where information from vmPFC, OFC, and ACC is combined in ventral striatum and conveyed to dorsal striatum via loops comprising midbrain nuclei. While goal-directed valuation depends on the integration of a vast amount of information, habitual valuation might circumvent this process and directly activate response representations being cached in dorsal striatum-motor cortex connections.

Crucially, the numerous neural adaptations to chronic alcohol misuse affect among other things the dopaminergic innervation of striatal medium spiny neurons (Volkow & Baler, 2014; Volkow, Wang, Tomasi, & Baler, 2013). These effects are assumed to drive the proposed shift from goal-directed to habitual alcohol use in AUD, because they "hijack" the normal dopaminergic signal cascade (Keramati & Gutkin, 2013).

1.3.3 Striatal adaptations associated with chronic alcohol consumption

Alcohol and other drugs of abuse have been shown to lead to long-lasting changes in the dopaminergic mechanisms in the midbrain and striatum. A long line of studies in the 1990s and 2000s have established that drugs of abuse have a direct or indirect enhancing effect on the phasic dopamine level released by VTA neurons (Volkow et al., 2002; Volkow, Fowler, Wang, Baler, & Telang, 2009; Volkow et al., 2013). In the striatum, where many of the dopaminergic neurons in the midbrain terminate, there are at least two main classes of medium spiny neurons – one is primarily equipped with excitatory D1 (dopamine) receptors, which have low dopamine affinity and enhance glutamatergic signaling, and the other class is primarily equipped with inhibitory D2 (dopamine) receptors, which have high affinity for dopamine and inhibit glutamatergic signaling (Surmeier et al., 2007; Volkow et al., 2013). Dopamine works here as a neuromodulator, that is, it influences ion channels in the dendritic membrane of the post-synaptic neuron and, thereby, modulates its excitability (Surmeier et al., 2007). Previous studies showed that repeated drug exposure leads to sensitization of D1 receptors and decreased signaling of D2 receptors (through desensitization, reduction in number of receptors, or both; Hietala et al., 1994; Thompson, Martini, & Whistler, 2010; Tupala et al., 2003; Volkow et al., 1996, 2002; Volkow, Fowler, Wang, Swanson, & Telang, 2007). This leads to an imbalance between the excitatory (presumably reinforcement-mediating) direct D1-mediated pathway and the inhibitory (presumably punishment-mediating) indirect D2-mediated pathway. Decreased D2 signaling and number of receptors is associated with impulsive behavior and decreased activity in OFC, ACC, and dlPFC (Volkow et al., 2006, 2013). Volkow and Baler (2014) elaborated this issue further: D2 receptors in

striatum are part of the inhibitory modulation of OFC, ACC, and dlPFC, which in turn are associated with salience attribution, inhibitory control and emotion regulation, and decision making, respectively. This might be the neural correlate of the increased motivational value of drugs of abuse and addicts' often increased levels of impulsivity (Volkow & Baler, 2014). It can be speculated that this is a possible causal chain: chronic alcohol use leads to a decrease of striatal D2 signaling which leads to insufficient downregulation of prefrontal areas which in turn leads to impulsive, reward-driven, or habitual behavior. But this may be only one side of the story: Volkow and colleagues have shown that persons being not dependent on alcohol despite many alcohol-dependent relatives had a higher number of D2 receptors in striatum (Volkow et al., 2006). The authors interpreted this as a possible protective mechanism against developing AUD (Volkow et al., 2009). This suggests that the basic level of D2 receptors in striatum may be a predisposing genetic factor influencing the susceptibility for developing AUD besides its role during development and maintenance of AUD.

These findings suggest the possibility that chronic alcohol abuse might lead behavioral control from being rather goal-directed to habitual through its influence on striatal dopamine function. At the same time, the initial level of dopamine receptors and their sensitivity before alcohol use might pose a risk factor for the emergence of AUD if being decreased or a protective factor if being increased for reasons of gene-environment interactions during development. Thus, in concert with the theoretical and empirical psychological work presented in section 1.2, it can be speculated that being at risk for the development of AUD before chronic alcohol use might be associated with a stronger tendency for habitual over goal-directed control due in part to the individual neurobiological setup of the striatum. As the same dopaminergic mechanism might account for trait-like impulsive choice biases, these biases might also precede AUD in at-risk individuals.

1.4 Synopsis and research questions

Previous studies have repeatedly found corroboration of the proposed shift from goal-directed to habitual control during (extended) training. This shift is accompanied by a neural-activation shift from dorsomedial (caudate) to dorsolateral striatum (putamen) during behavioral control. In addition, the shift has been shown to advance even faster with drugs of abuse involved as outcome of the instrumental learning itself or just applied unrelated to the training. Adaptions of receptor sensitivity or quantity in striatum might be the neural mechanism behind the accelerated shift when drugs of abuse are involved. This relates to the assumption that chronic alcohol use in AUD is accompanied by a shift from goal-directed to habitual alcohol consumption and probably even a shift in general, alcohol-unrelated behavioral control towards automatic, habitual strategies. In addition, the influence of specific salient features of choice options, like the delay, risk, and valence of the associated outcomes, is presumed to be altered in AUD and may affect valuation and, therefore, behavioral control in VBDM. But evidence of these phenomena in humans is weaker than in rodents and monkeys and the question of cause or consequence of chronic alcohol use is still not sufficiently answered. Moreover, interindividual differences in the setup of neural reward-processing circuits and their functionality give rise to the question whether alterations in VBDM might even precede the onset of pathological alcohol use and pose a risk factor for the development of AUD.

The aim of this thesis is to further elucidate the associations between alcohol consumption and VBDM. For that purpose, two cohorts of participants were examined: first, a sample of 201 healthy 18-year-old male social drinkers to examine these associations before prolonged alcohol abuse could lead to severe neural and behavioral adaptations. In this sample, henceforth called Sample 1, the question whether changes in VBDM processes may precede the onset of pathological alcohol use and even predict non-pathological consumption was investigated. Second, a sample of 114 AUD patients and 98 matched control participants was examined to shed light on these relations in the pathological state. Furthermore, analyses comprised data from the baseline assessment (cross-sectional analyses) and the twelve-month follow-up interval (longitudinal analyses). Specifically, in the presented studies I want to add insights about the following questions:

I. Association of alcohol consumption with goal-directed and habitual behavioral control

1. Is the balance between goal-directed and habitual control associated with alcohol consumption and its change within one year in young-adult social drinkers (Study 1/Chapter 2) and might, therefore, pose a predisposing risk factor for alcohol use per se and its escalation?

2. Is the balance between goal-directed and habitual control associated with alcohol consumption and predictive of relapse rates in AUD patients (Study 2/Chapter 3)?

II. Association of alcohol consumption with the appraisal of modulating features of VBDM, that is, delay, risk, and valence

3. Is the appraisal of known modulators of the valuation systems in VBDM (i.e. delay, risk, and valence) related to alcohol consumption and its change within one year in young-adult social-drinkers (Study 3/Chapter 4) and might, therefore, pose a predisposing risk factor for alcohol use per se and its escalation?

4. Is the appraisal of known modulating features of option valuation in VBDM (i.e. delay, risk, and valence) related to alcohol consumption and predictive of relapse rates in AUD patients (Study 3/Chapter 4)?

Chapter 2. Study 1

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2.1 Abstract

Alcohol dependence is a mental disorder which has been associated with an imbalance in behavioral control favoring model-free habitual over model-based goal-directed strategies. It is as yet unknown, however, whether such an imbalance reflects a predisposing vulnerability or results as a consequence of repeated and/or excessive alcohol exposure. We, therefore, examined the association of alcohol consumption with model-based goal-directed and model-free habitual control in 188 eighteen-year-old social drinkers in a two-step sequential decision-making task while undergoing functional magnetic resonance imaging (fMRI) before prolonged alcohol misuse could have led to severe neurobiological adaptations. Behaviorally, participants showed a mixture of model-free and model-based decision-making as observed previously. Measures of impulsivity were positively related to alcohol consumption. In contrast, neither model-free nor model-based decision weights nor the tradeoff between them were associated with alcohol consumption. There were also no significant associations between alcohol consumption and neural correlates of model-free or model-based decision quantities in either ventral striatum or ventromedial prefrontal cortex. Exploratory whole-brain fMRI analyses with a lenient threshold revealed early onset of drinking to be associated with an enhanced representation of model-free reward prediction errors in the posterior putamen. These results suggest that an imbalance between model-based goal-directed and model-free habitual control might rather not be a trait marker of alcohol intake per se.

2.2 Introduction

The underlying mechanisms of developing alcohol dependence are not fully resolved despite extensive research over the past decades (e.g. Huys, Deserno, Obermayer, Schlagenhauf, & Heinz, 2016; Redish et al., 2008). Among numerous theoretical approaches, a dual-systems account has been used to explain the development of alcohol dependence (Everitt & Robbins, 2013). In this account, alcohol consumption is assumed to be initially goal-directed, that is, characterized by knowledge of the contingency between an action (e.g. alcohol intake) and its consequence (e.g. relaxation, euphoria) and an incentive (motivational) value of this consequence. However, it has been argued that with successive repetitions alcohol consumption may first become stimulus-driven and dissociated from its actual consequences, referred to as habitual, and later on compulsive (Everitt & Robbins, 2013; Tiffany, 1990). In general, these dual-systems accounts hypothesize goal-directed and habitual control to concur and be implemented in separate but interacting and/or competing neural circuits (Dolan & Dayan, 2013; Huys, Tobler, Hasler, & Flagel, 2014).

The standard approach to investigate goal-directed and habitual behavior experimentally is by using outcome-devaluation paradigms (e.g. Adams and Dickinson, 1981; de Wit et al, 2007). Goal-directed control can adapt behavior to changes in the value of an outcome before experiencing the action-outcome association, whereas habitual control needs to experience the devalued outcome before being able to adapt. The distinction between goal-directed and habitual choices maps onto a theoretical distinction between prospective model-based and retrospective model- free valuation. The 2-Step task, a two-stage Markov decision problem (Daw et al, 2011), operationalizes this distinction and putatively allows the two components to be measured in humans (Daw et al., 2005; Dolan & Dayan, 2013; Friedel et al., 2014; Gillan, Otto, Phelps, & Daw, 2015).

In model-free RL, subjective values for state-action pairs are updated by RPEs, which encode the difference between expected and received outcomes (Schultz & Dickinson, 2000; Sutton & Barto, 1998). This updating process happens when an action-outcome association is experienced and typically needs multiple repetitions to change state-action values and thereby action policies. Therefore, model-free RL shares its retrospective, inflexible, but computationally cheap nature with habitual behavioral control. In contrast, model-based RL builds an internal model of the environment and plans actions by searching the potential combinations of future actions and outcomes. Via changes to the model, it can flexibly adapt to changes in contingencies and values along the paths of the internal model. These qualities match the operant definition of goal-directed control.

Reward prediction errors result in a phasic activation of dopamine midbrain neurons (D'Ardenne, McClure, Nystrom, & Cohen, 2008; Schultz, 1997) as well as dopamine-innervated target areas such as the ventral striatum and vmPFC (Daw et al., 2011). Although these phasic signals conform to exacting detail with model-free theory predictions (for a review, see Huys et al, 2014), the RPE signals in vS also incorporate model-based valuations providing a path by which model-based predictions can be incorporated retrospectively into model-free predictions (Daw et al., 2011; Gershman, Markman, & Otto, 2014; Sadacca, Jones, & Schoenbaum, 2016).

There are suggestions that the balance between habitual and goal-directed control might be shifted towards habitual behavior in alcohol dependent patients. (Sjoerds et al, 2013) used an outcome-devaluation task. Although there was no behavioral evidence for a shift (patients just performed worse in all conditions), there was a suggestive decreased activation in vmPFC and ventral striatum during putatively goal-directed and increased activation of the putamen during putatively habitual decisions in the patients. In the 2-Step task, Sebold et al. (2014) reported an impairment of model-based decision-making after losses in alcohol-dependent patients compared to healthy control participants. Gillan et al. (2016) also reported a decrease in model-based decision-making to be associated with Alcohol Use Disorder Identification Test (AUDIT) scores. However, Voon et al. (2014) found no difference between detoxified alcohol-dependent patients and healthy controls. Of note, all of these results test decision-making without reference to the abused substance and as such speak to a generalized shift in decision-making rather than one limited to the setting of the substance (Everitt & Robbins, 2013).

Alterations in patients could either be a consequence of prolonged alcohol abuse and corresponding neurobiological adaptations (Heinz et al., 2009; Volkow, Fowler, Wang, & Swanson, 2004) or reflect a predisposition for aberrant decision-making preceding the development of hazardous drinking behavior. Another possible explanation combines both aspects: Aberrant decision-making may lead to early and numerous encounters with drugs of abuse, their high reward value leads to fast habitization of drug seeking and consumption including neurobiological adaptations in cortico-basal ganglia circuits. This might shift the balance further toward aberrant decision-making processes (cf. Sjoerds et al., 2013; Story, Vlaev, Seymour, Darzi, & Dolan, 2014).

We aimed to investigate the association of model-based and model-free decision-making with alcohol consumption before prolonged alcohol misuse could have led to severe neurobiological adaptations. Therefore, we sampled 18-year old social drinkers, assessed their

alcohol consumption, and had them perform the 2-Step task. We hypothesized that a shift towards model-free habitual and away from model-based goal-directed behavior and neural correlates thereof would be associated with greater alcohol consumption. In particular, we tested whether participants with (i) stronger model-free or (ii) weaker model-based control during 2-Step and (iii) stronger model-free RPE-related BOLD signals of ventral striatum and vmPFC or (iv) weaker model-based signatures there are associated with (1) greater alcohol consumption in general and, specifically, with (2) earlier onset of drinking, (3) higher average alcohol intake, (4) the presence of binge-drinking and more frequent and heavy binge-drinking events, (5) higher scores on drinking-related questionnaires, and (6) elevated levels of blood markers for liver function and alcohol consumption.

2.3 Material and methods

2.3.1 Participants and procedure

Two hundred one 18 year-old male social drinkers completed the first assessment of a longitudinal fMRI study (ClinicalTrials.gov identifier: NCT01744834). They were randomly sampled from the population of 18 year-old men of two German cities (Berlin, Dresden) by the respective local registration office. Subjects who responded to the invitation letter were screened via telephone. Exclusion criteria were a history of or current neurological or mental disorders (except for nicotine dependence and alcohol abuse), left-handedness, and contraindications for MRI. Participants had to have normal or corrected-to-normal vision. Women were not included because they show decreased rates of risky alcohol consumption compared to men (Pabst & Kraus, 2008). An additional inclusion criterion was for participants to have had at least two drinking occasions in the past three months.

Participants came in twice. At the first appointment, they gave written informed consent and were interviewed using the Composite International Diagnostic Interview (CIDI; Jacobi et al., 2013; Wittchen & Pfister, 1997) to assess mental disorders according to the German version of the DSM-IV-TR (Saß, Wittchen, Zaudig, & Houben, 2003). Further, participants completed several questionnaires. They returned for the second appointment approximately nine days later (SD=16d) to complete the 2-Step task (Daw et al, 2011) during fMRI. Blood samples for analysis of alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (γ-GT), and phosphatidylethanol (PEth) were drawn on the first (Berlin) or second (Dresden) appointment. This study was approved by local ethics committees of Technische Universität Dresden and Charité Universitätsmedizin Berlin.

Behavioral analyses are based on 188 subjects. Participants were excluded due to CIDI diagnosis of alcohol dependence (n=1), alcohol abstinence in the past year though stated otherwise during telephone screening (n=2), positive drug screening on the day of the fMRI assessment (n=7), and missing 2-Step data due to technical issues (n=3). Effect size estimates of previous studies regarding model-free/-based control and alcohol range from |d|=.06 (Voon et al, 2014) over |d|=.12 (Gillan et al, 2016) to |d|=.53 (Sebold et al, 2014) for which we would have a power to identify an association of (1-β)=.07 , (1-β)=.12, and (1-β)=.94, respectively (with N=188 and α=.05). To check whether exclusion criteria influenced results, all behavioral analyses were repeated with all available data (n=198).

2.3.2 Measures of goal-directed and habitual behavioral control

The Two-Step task consisted of 201 trials, each of which was composed of two subsequent binary choices (Figure 3). First-stage stimuli were always the same two grey boxes. Choice of one of them led with a probability of 70% (common transition) to one colored pair of 2nd-stage stimuli and with 30% (rare transition) to the other (vice versa for the alternative 1st-stage stimulus). Participants were informed about the transition structure and that transition probabilities stay fixed during the experiment. Each 2nd-stage stimulus led to reward (20 Cent) with a probability between 25% and 75%, which was slowly changing during the course of the experiment according to Gaussian random walks (the exact same random walks as in the original publication by Daw et al., 2011, were used). With this setup, participants had to constantly update the utilities of the 2nd-stage stimuli. Updating the values of 2nd-stage stimuli relies on model-free learning as there is no further transition to another state. Therefore, model-based and model-free control had the same 2nd-stage values but produced different values at the 1st stage. Choices at the 1st stage were modeled as a mixture of model-free and model-based control: model-free control increased the probability of repeating a choice at the 1st stage after being rewarded at the second stage regardless of the transition type of the respective trial; model-based control computes action values by weighting the values of possible future states with the probability to reach this state. Hence, model-based control is sensitive to which transition had occurred. Participants were paid out the collected rewards of a randomly chosen third of all trials and were told so before the experiment.

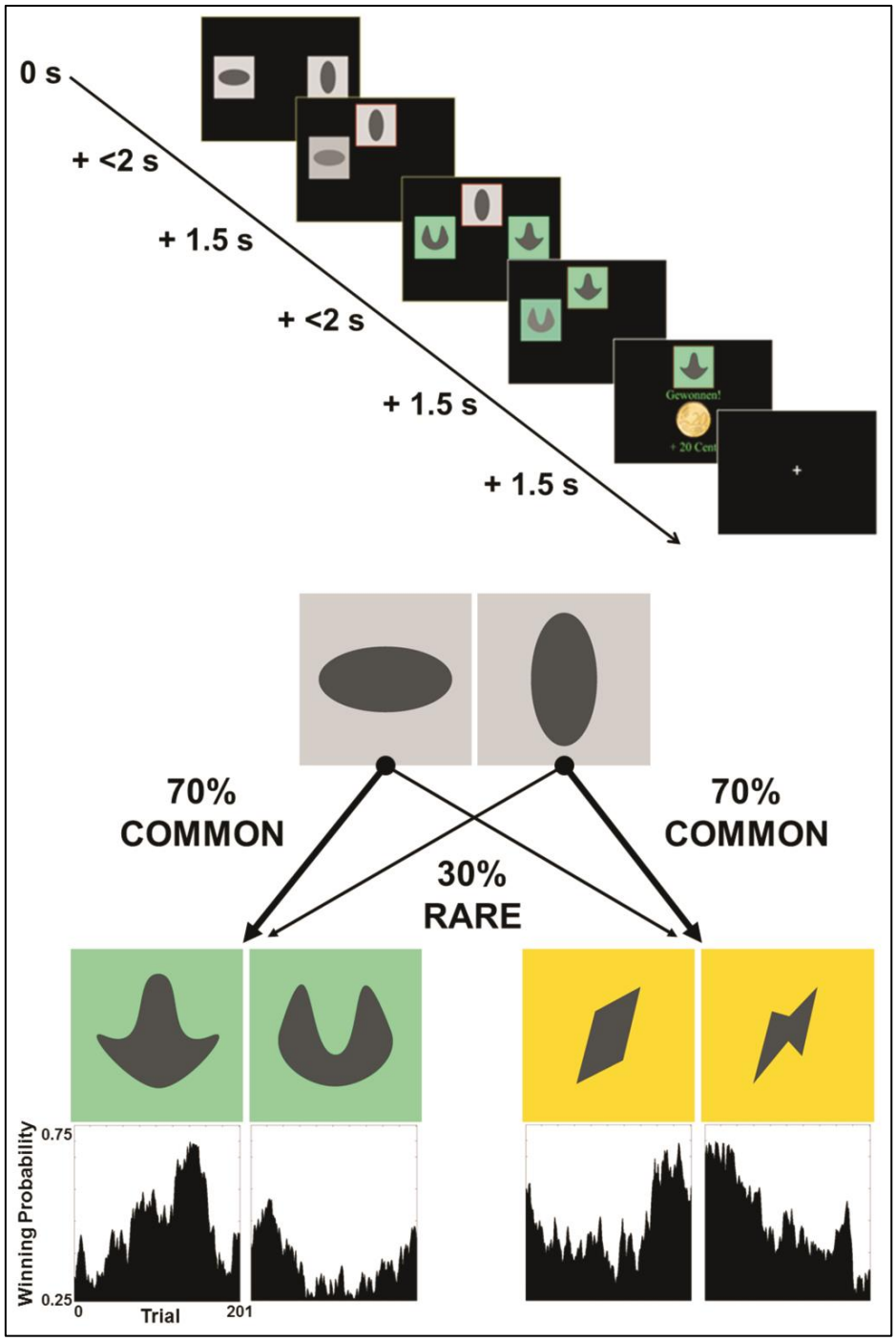

Figure 3. Upper panel: Temporal sequence of one trial of the Two-Step task starting with presentation of the two gray first-stage stimuli followed by a response phase of maximum 2 seconds. Then second-stage stimuli were presented (either green or yellow pair), followed by another response phase, outcome presentation and finally an intertrial interval with an exponentially distributed jitter of 1–7 seconds. Lower panel: Schematic view of the design of the Two-Step task displaying the choices on the first stage (gray stimuli) and second stage (green and yellow stimuli); displayed below the second-stage stimuli are the corresponding winning probabilities of each second-stage stimulus and their change during the course of the 201 trials of the experiment.

Choice data were analyzed using hierarchical logistic mixed-effects regression implemented in the lme4 package (version 1.1-10; Bates, Mächler, Bolker, & Walker, 2015) in R (version 3.2.2; R Development Core Team, 2008). Repetition of 1st-level choice was

predicted by previous trial's outcome (rewarded vs. unrewarded) and transition probability (common vs. rare). Both factors and their interaction were taken as random effects across subjects. A significant main effect of outcome indicated a model-free strategy, whereas a significant interaction of outcome and transition probability indicated model-based control (Daw et al, 2011). To test for associations with alcohol consumption, measures of drinking behavior were included as additional between-subject factors in the regression analysis. In addition, scores for model-free (MF_{score}) and model-based control (MB_{score}) were derived from the individual probabilities to repeat 1st-stage choice (stay probabilities). These scores are calculated according to the respective assumed choice pattern in model-free and model-based control [(MF_{score} = P(stay|rewarded common) + P(stay|rewarded rare) - P(stay|unrewarded common) - P(stay|unrewarded rare); MB_{score} = P(stay|rewarded common) - P(stay|rewarded rare) - P(stay|unrewarded common) + P(stay|unrewarded rare); Sebold et al, 2014]. Furthermore, choice data were fitted by the computational model introduced by Daw et al. (2011), which assumes a hybrid controller using goal-directed and habitual choice strategies. In the model, goal-directed choices were accounted for by model-based RL, assuming correct weighting of expected outcomes with expected transition probabilities. The habitual learning system was implemented as model-free SARSA(λ) TD learning (Rummery & Niranjan, 1994). Both systems were assumed to contribute to behavioral choice according to the relative weight parameter ω, which varies between fully model-free (ω=0) and fully model-based (ω=1) choice (see Appendix A.1.1 for details). There were six further parameters of choice behavior modeled, but due to our specific focus on goal-directed and habitual control, we did not analyze these here. We applied a logistic transformation to ω (creating ω_{log}) to adhere to normal distribution assumptions during model fitting and parametric statistical testing. Individual estimates of ω_{log} were used as indicator for the balance of model-free and model-based control in addition to MF_{score} and MB_{score}. Model comparisons replicated the superiority of a hybrid controller over pure model-free and pure model-based strategies for the whole sample. Individually, 74% (n = 139) subjects showed model fits better than chance.

2.3.3 Measure of alcohol consumption

To characterize participants' drinking behavior, we used information acquired with the CIDI (Jacobi et al, 2013; Wittchen and Pfister, 1997): age of 1st drink (i.e. drinking a whole alcoholic beverage), age of 1st time being drunk, estimated average alcohol consumption in past year (g alc/day), average alcohol consumption per drinking occasion in the past year (g

alc), age of 1st binge-drinking event, number of binge-drinking events lifetime, and average alcohol consumption per binge-drinking event in the past year (g alc). Binge-drinking was defined as the consumption of at least five drinks (≥ 60 g alc) on one occasion. To increase reliability of the single CIDI items as indicators of alcohol drinking behavior and to account for their high intercorrelations (see Table 1), we calculated a sum score ($Drink_{score}$) from the z-scaled CIDI items with higher values indicating greater alcohol consumption (see SM1.2 for details). 74% of the sample (n = 139) reported at least one lifetime binge drinking episode. Binge-drinkers and non-bingers can be seen as two meaningful subgroups within our sample of social drinkers systematically differing in their alcohol consumption (Table S 5) and were, therefore, compared regarding measures of goal-directed and habitual control.

Additionally, we used blood markers for alcohol intake and liver function (AST, ALT, γ-GT, PEth) and several questionnaires to characterize drinking behavior: the Alcohol Dependence Scale (ADS; Horn, Skinner, Warnberg, Foster, & the Alcoholism and Drug Addiction Research Foundation, 1984), Obsessive Compulsive Drinking Scale (OCDS-G; K. Mann & Ackermann, 2000), and adapted forms of the Family Tree Questionnaire (FTQ; R. E. Mann, Sobell, Sobell, & Pavan, 1985) and the alcohol-related section of the Family History Assessment Module (FHAM; Rice et al., 1995). Using FTQ and FHAM, participants were classified as family history positive if they had at least one first-degree alcohol-dependent relative fulfilling three or more lifetime DSM-IV-TR criteria or had any treatment of alcohol dependence. 3.7% of our sample were considered family-history positive. Due to this small proportion, family history was not included in our analyses. $Drink_{score}$ correlated highly significant with each other measure of alcohol consumption (Bonferroni corrected for multiple comparisons (105 tests), all ps < .0005) except for the blood markers AST, ALT, γ-GT, and PEth (all ps > .045; Table 1).

2.3.4 Behavioral statistical analyses

To examine associations between the multiple measures of goal-directed and habitual behavioral control (ω_{log}, MF_{score}, MB_{score}) and of alcohol consumption (CIDI measures including $Drink_{score}$, ADS sum score, OCDS-G sum score, and blood markers), we first performed a multivariate analysis of variance (MANOVA) with measures of drinking behavior ($Drink_{score}$, ADS sum score, OCDS-G sum score, and blood markers) as dependent and measures of goal-directed/habitual behavioral control (ω_{log}, MF_{score}, MB_{score}) as independent variables. We used MANOVA because our multiple outcome measures

characterizing drinking behavior are intercorrelated and by using a multivariate approach we control the familywise error rate. This analysis was repeated with measures of impulsivity as independent variables. The Sum score of the Barratt Impulsiveness Scale short form (BIS-15; Meule, Vögele, & Kübler, 2011) and the Impulsivity subscale of the Substance Use Risk Profile Scale (SURPS; Woicik, Stewart, Pihl, & Conrod, 2009) were also included in behavioral analyses. Thereby, we tested the association between measures of alcohol consumption and measures of impulsivity, which were previously related to alcohol dependence and onset of consumption (Jurk et al., 2015; Stanford et al., 2009). Testing the association of alcohol consumption and impulsivity was used as demonstration that our analytic approach was sensitive to detecting associations in our data. In addition, we select the best predictors of drinking behavior (operationalized with $Drink_{score}$) with an elastic net analysis, performed with the glmnet package (version 2.0-2; J. Friedman, Hastie, & Tibshirani, 2010) implemented in R (see Appendix A.3.4). This type of analysis selects predictors in order to build a regression model explaining as much variance of the outcome as possible with the least necessary number of predictors. Measures of goal-directed/habitual control and impulsivity were entered as predictors to test whether one construct is superior to the other in predicting $Drink_{score}$. Next, we used a correlational approach. Exact Kolmogorov-Smirnov tests implied violation of the assumption of normality for most measures of goal-directed/habitual control and alcohol consumption (Table 2). Therefore, reported correlation coefficients are Spearman's ρ, which was shown to have smaller alpha error rate and higher power than Pearson's r in case of non-normal variables and large sample sizes (Bishara & Hittner, 2012). Last, we compared binge-drinkers and non-bingers and the four risk groups regarding WHO criteria of alcohol consumption (World Health Organization, 2000) in regard to their measures of goal-directed/habitual behavioral control. In response to comments of the reviewers, we additionally examined whether high self-reported impulsivity is associated with increased habitual or decreased goal-directed behavioral control and neural correlates thereof as reported recently (Deserno, Wilbertz, et al., 2015). Thus, we correlated self-report measures of impulsivity (BIS-15) with measures of habitual/goal-directed control and neural correlates thereof.

All analyses regarding data distribution, correlations, and MANOVAs were performed with SPSS 23.0 (2015, IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.).

2.3.5 Functional magnetic resonance imaging data acquisition and analysis

Imaging data were obtained using 3-Tesla whole-body MRI scanners (Magnetom Trio, Siemens, Erlangen, Germany) equipped with a 12-channel head coil located at the Neuroimaging Center, Technische Universität Dresden, and the Charité Universitätsmedizin Berlin. For fMRI, a standard T2*-weighted echo-planar imaging (EPI) sequence (TR = 2410 ms; TE = 25 ms; flip angle: 80°; voxel size:3 x 3 x 2 mm (1 mm gap); FOV:192 x 192 mm; in-plane resolution:64 x 64 pixels) was obtained comprising 42 transversal slices in descending order, orientated approximately 25° to the anterior commissure-posterior commissure line. Moreover, a structural T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) image was obtained (TR = 1900 ms, TE = 2.52 ms, flip angle: 9°, voxel size:1 x 1 x 1 mm, FOV: 256 x 256 mm).

FMRI preprocessing and data analyses were performed with Statistical Parametric Mapping software (SPM8; London, UK: Wellcome Department for Imaging Neuroscience) implemented in Nipype Version 0.9.2 (Gorgolewski et al., 2011) and Matlab R2014a (2014. Natick, MA: The MathWorks Inc.). Preprocessing included correction for differences in slice acquisition times with reference to the middle slice, motion correction via realignment of each slice to the first, correction for field inhomogeneities with a voxel displacement map computed from acquired field maps, coregistration of the mean EPI image to the individual MPRAGE image, segmentation and normalization of the individual MPRAGE image to Montreal Neurological Institute (MNI) space and applying these normalization parameters to the distortion-corrected EPI images, simultaneously resampling EPI images to 2 x 2 x 2 mm, and spatially smoothing the EPI images with a Gaussian kernel of 8 mm full-width-half-maximum. During first-level analyses, a high-pass filter of 128 s width was applied.

Model-based fMRI analyses are based on 146 subjects. Neuroradiologists screened each T1-weighted MPRAGE image for anatomical findings leading to exclusion of five participants. Additionally, participants were excluded due to missing field maps (n = 3), ghost artifacts in EPI after preprocessing (n = 4), non-remediable failure of coregistration (n = 2) or normalization (n = 7), and extensive motion during fMRI (n = 21; > 3 mm translation or 3° rotation volume-to-volume) resulting in a sample size of n = 146 for fMRI analyses. We computed RPEs for each participant. RPEs are non-zero at the onsets of 2^{nd}-stage and outcome presentation (Daw et al, 2011). Therefore, we modeled BOLD signals at these time points by two parametric modulators obtained from the computational model. Model-free RPE (RPE_{MF}) and model-based RPE time series were derived for both time points under the assumption of fully model-free ($\omega = 0$) and fully model-based ($\omega = 1$) control, respectively.

To capture unique trial-variance in RPEs associated with the model-based but not the model-free system, we used the difference between model-free and model-based RPEs ($RPE_{\Delta MB}$) as regressor. At the 2nd stage, there is no further transition to another stage and model-based learning reduces to pure model-free learning. That is why $RPE_{\Delta MB}$ is zero at outcome presentation. We set up individual fMRI statistics according to Daw et al. (2011; see Appendix A.2.1 for details). For repetition of their analyses, we validated the task setup with region of interest (ROI) analyses in anatomically defined masks of bilateral ventral striatum and vmPFC (Appendix A.2.2, Figure S 1); reported activations were deemed significant at $p_{FWE}<.05$ for the peak voxel. To test our hypotheses that neural correlates of model-free and model-based control are associated with alcohol consumption, mean activation in the same ROIs were correlated with measures of drinking behavior (trading-off spatial resolution to reduce the number of tests performed). Additionally, exploratory whole-brain analyses were performed to test for associations outside the a priori defined ROIs. For these analyses, statistical thresholds were set to $p_{uncorr.} < .001$, $k \geq 50$, and results were deemed significant with $p_{FWE} < .01$ on cluster level. All fMRI analyses included a dichotomous variable for site of investigation as covariate to control for possible center effects.

Table 1. Intercorrelation of measures of alcohol consumption (n = 188).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Drink score	Age of 1st drink	Age of 1st time drunk	Estimated alcohol consumption in past year (g/day)	Alcohol consumption in past year (g/drinking occasion)	Age of 1st binge-drinking episode	Number of binge-drinking episodes lifetime	Alcohol consumption per binge-drinking episode (g)	ADS Sum Score	OCDS-G Sum Score	AST	ALT	γ-GT	PEth
1	1	-.500†	-.617†	.707†	.713†	-.422†	.843†	.756†	.477†	.274†	-.036	.129	.082	.14
2		1	.538†	-.187*	-.121	.123	-.227**	-.186*	-.233**	-.06	-.073	-.111	-.129	-.117
3			1	-.311†	-.276†	.300†	-.282†	-.286†	-.317†	-.144	-.036	-.115	-.042	-.037
4				1	.728†	-.034	.669†	.557†	.384†	.378†	-.009	.026	.008	.375†
5					1	-.025	.695†	.632†	.420†	.249†	-.014	.011	-.043	.149
6						1	-.362†	.04	-.142	.046	.002	-.127	.037	.114
7							1	.646†	.443†	.302†	-.027	.124	.046	.118
8								1	.405†	.213**	-.079	.043	.06	.132
9									1	.489†	.018	-.049	-.088	.154
10										1	.096	.041	-.019	.162*
11											1	.566†	.124	.079
12												1	.377†	.049
13													1	.124
14														1

Note: ADS = Alcohol Dependence Scale. ALT = alanine transaminase. AST = aspartate transaminase. $Drink_{score}$ = score of drinking behavior from CIDI measures of alcohol consumption. γ-GT = gamma-glutamyl transferase. OCDS-G = Obsessive Compulsive Drinking Scale. PEth = phosphatidylethanol.
* $p < .05$ (two-tailed). ** $p < .01$ (two-tailed). † $p < .001$ (two-tailed). All correlations are Spearman's ρ

2.4 Results

2.4.1 Sample characteristics

The sample consisted of 188 young male adults. Table 2 summarizes the distribution of sociodemographic information and relevant measures of goal-directed/habitual control and alcohol consumption. According to criteria for risk of alcohol consumption published by the WHO (World Health Organization, 2000) for comparative research purposes, this sample can be characterized as follows: regarding average consumption on a single drinking occasion in the past year, 21.8% fall into the low-risk (1-40 g alc), 31.9% in the medium-risk (41-60 g alc), 30.3% in the high-risk (61-100 g alc), and 16.0% in the very-high-risk category (101+ g alc); regarding average alcohol consumption per day in the past year, 96.8% have to be characterized as having low-risk (1-40 g alc), 2.1% as having medium-risk (41-60 g alc), and 1.1% as having high-risk (61+ g alc) alcohol consumption. Eight participants (4.3%) fulfilled DSM IV-criteria of alcohol abuse. 73.9% reported at least one occasion of binge-drinking. Levels of blood markers were below the cut-off value for pathological levels in 91.5% (AST; cut-off 0.835 µKat/l), 93.1% (ALT; cut-off 0.835 µKat/l), and 100% (γ-GT; cut-off 1.002 µKat/l) of the sample. PEth values were available for 158 participants only, because collection started three months after the start of 2-Step data collection. Of available PEth data, 31.6% were negative (i.e. < 20 ng/ml) suggesting no or very low alcohol consumption in the preceding two weeks; in 46.8%, values were positive but too low to be exactly measurable (i.e. 20-100 ng/ml) indicating low alcohol intake. For these participants, PEth values were set to 10 and 60, respectively. Consequently, PEth was treated as ordinal data. Thirteen participants (8.2%) had PEth values > 210 ng/ml, which was suggested to be the threshold between moderate drinking and alcohol misuse (Wurst et al., 2015).

Thirty participants (16%) reported to currently be regular smokers. Exact Mann-Whitney U-tests showed no differences in measures of goal-directed/habitual control between smokers and non-smokers. Also, smoking status had no significant effect on the results of analyzing stay probabilities with the logistic regression. In addition, we compared participants with an individual better-than-chance model fit (n = 139) with the non-fitters regarding the measures of alcohol consumption with exact Mann-Whitney U-tests and found no significant differences. Furthermore, there were no significant correlations between individual log-likelihoods and measures of alcohol consumption (all Spearman's $\rho < |.135|$, all ps > .067) except for correlations with the three blood markers (AST: $\rho = .156$, $p = .035$; ALT: $\rho = .174$, $p = .019$; γ-GT: $\rho = .168$, $p = .023$).

Table 2. Demographic information, descriptive statistics of measures of goal-directed/habitual control and alcohol consumption of participants included in analyses (n = 188; see Table S 1 for these data of the complete sample).

	n	Min	1st quartile	Mdn	3rd quartile	Max
Descriptive statistics of sample						
Age	188	18.07	18.24	18.33	18.50	18.93
Years in school	187	4	11	12	12	15
Measures of goal-directed/habitual control						
ω[1]	188	0.00	0.20	0.59	0.80	1.00
MF_{score}	188	-0.42	-0.04	0.08	0.21	0.85
MB_{score}	188	-0.34	0.06	0.24	0.49	1.21
Measures of alcohol consumption						
CIDI measures						
$Drink_{score}$	188	-8.21	-3.54	-0.35	1.61	17.52
Age of 1st drink[1]	188	9	14	14	15	18
Age of 1st time drunk[1]	180	10	15	16	17	18
Estimated alcohol consumption in past year (g/day) [1]	188	0.00	3.21	6.43	15.43	112.50
Alcohol consumption in past year (g/drinking occasion) [1]	188	18	45	54	90	342
Age of 1st binge-drinking episode[1]	131	14	16	16	17	18
Number of binge-drinking episodes lifetime[1]	131	1	4	10	20	150
Alcohol consumption per binge-drinking episode (g) [1]	139	63	90	117	135	450
Questionnaire measures						
ADS sum score[1]	181	0	2	4	7	30
OCDS-G sum Score[1]	183	0	1	3	5	18
Blood markers						
AST (µKat/l) [1]	183	0.17	0.35	0.40	0.48	2.51
ALT (µKat/l) [1]	182	0.11	0.27	0.35	0.45	1.59
γ-GT (µKat/l) [1]	183	0.13	0.23	0.27	0.33	0.89
PEth[1]	158	10	10	60	60	1180
Measures of impulsivity						
BIS-15 sum score	185	18	27	30	34	45
SURPS Impulsivity [1]	186	5	9	10	11	17

Note: ADS = Alcohol Dependence Scale. ALT = alanine transaminase. AST = aspartate transaminase. BIS-15 = Barratt Impulsiveness Scale (short form). $Drink_{score}$ = score of drinking behavior from CIDI measures of alcohol consumption. γ-GT = gamma-glutamyl transferase. MB_{score}= score of model-based control. MF_{score} = score of model-free control. OCDS-G = Obsessive Compulsive Drinking Scale. ω = balance between model-free and model-based control. PEth = phosphatidylethanol. SURPS = Substance Use Risk Profile Scale.

2.4.2 Behavioral results

First, we analyzed behavioral choice tendencies of participants to find evidence for model-free and model-based control. Therefore, we performed a logistic regression to analyze how previous trial's transition type from 1st to 2nd stage (common vs. rare) and final outcome (reward vs. no reward) affected the probability to repeat the same choice at 1st stage in the current trial. Participants had a higher probability to repeat a 1st-stage choice after having been rewarded in the previous trial (significant main effect of outcome), which indicates model-free control strategies. The probability to repeat a 1st-stage choice was also increased after rewarded trials with common transition and unrewarded trials with rare transition (significant interaction effect of outcome and transition type). This interaction effect indicates model-based behavioral control. Additionally, this analysis yielded a significant main effect of transition with repetition probability being generally higher after common compared to rare transition trials (all *p*s < .001; see Appendix A.3.2 and Figure 5).

Second, we investigated the relationship between measures of goal-directed/habitual control and alcohol consumption. Therefore, we first included $Drink_{score}$ as additional between-subjects factor in the logistic regression analysis of choice repetition. This yielded no significant effects of $Drink_{score}$ while preserving the aforementioned main and interaction effects (see Appendix A.3.2). Then, we used MANOVA with measures of goal-directed/habitual control (ω_{log}, MF_{score}, MB_{score}) as independent and measures of alcohol consumption ($Drink_{score}$, ADS sum score, OCDS-G sum score, AST, ALT, γ-GT, PEth) as dependent variables. MANOVA is a multivariate approach bypassing the multiple comparisons problem we face with our multitude of dependent and independent variables. This analysis yielded no significant associations of alcohol consumption measures with ω_{log} ($F(7, 142) = 1.685$, $p = .117$, $\eta_p^2 = .077$), MF_{score} ($F(7, 142) = .646$, $p = .717$, $\eta_p^2 = .031$), or MB_{score} ($F(7, 142) = 1.491$, $p = .175$, $\eta_p^2 = .068$). Next, we correlated measures of goal-directed/habitual control (ω_{log}, MF_{score}, MB_{score}) with measures of alcohol consumption. The associations of main interest between $Drink_{score}$ and each measure of model-free/-based control did not reach significance (Table 3, Figure 5). Besides this, these analyses yielded a significant negative association of γ-GT with MB_{score} (Spearman's $\rho = -.160$, $p = .031$; Table 3). However, this finding does not survive Bonferroni correction for multiple comparisons (42 tests). No further correlation on the behavioral level reached significance (all *p*s > .168).

Since binge-drinkers and non-bingers can be seen as meaningful subgroups in this sample showing numerous differences in drinking behavior (Table S 5), we compared the measures of goal-directed/habitual control between these groups using Exact Mann-Whitney

U-tests. These analyses yielded no significant differences between binge-drinkers and non-bingers with regard to ω, MF_{score}, or MB_{score} (all *p*s > .125; Table S 5). In addition, we compared measures of goal-directed/habitual control between the four risk groups regarding average consumption on a single drinking occasion in the past year (World Health Organization, 2000). Adding WHO risk group as a fixed between-subjects factor in the logistic regression of stay probabilities did not yield any significant effect of WHO risk group while preserving aforementioned main and interaction effects. Non-parametric Kruskal-Wallis Tests showed no differences between the WHO risk groups in ω, MF_{score}, or MB_{score} (all $\chi^2(3) < 2.584$, *p*s > .460).

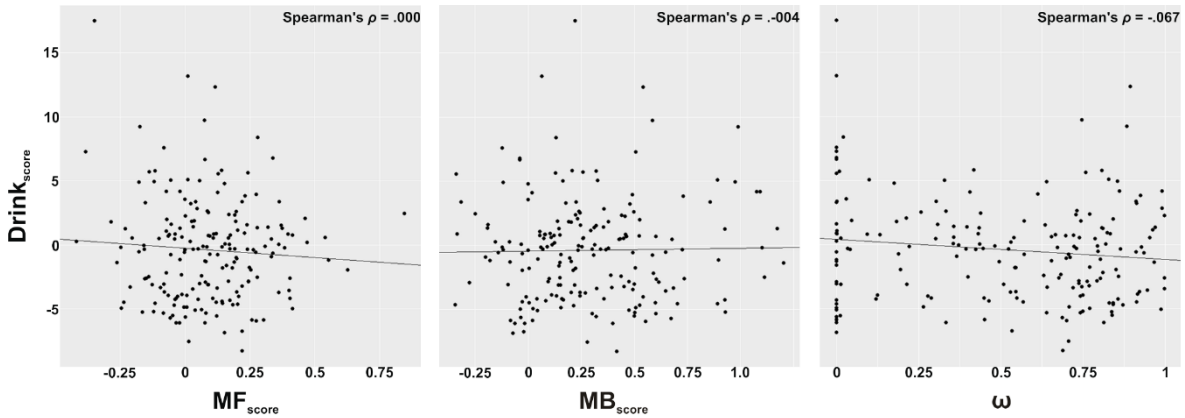

Figure 4. Scatterplots of $Drink_{score}$ with the three measures of goal-directed/habitual control: the score for model-free (MF_{score}) and model-based (MB_{score}) choice behavior stay probabilities and the balance parameter from the hybrid-controller computational model (ω). Note that for displaying purposes and better interpretability, ω is used instead of ω_{log}, but this does not influence the rank–order correlation.

In contrast to model-free and model-based control, measures of impulsivity (BIS-15 sum score, SURPS impulsivity subscale) showed the anticipated associations with drinking behavior. Correlational analyses yielded several significant results indicating that earlier and heavier alcohol consumption is associated with higher scores of impulsivity (Table 3). To directly compare the associations of measures of goal-directed/habitual control and impulsivity with measures of drinking behavior, we set up a MANOVA including both groups of predictors. This analysis corroborated previous results by revealing significant associations with measures of impulsivity but not goal-directed/habitual control (ω_{log}: ($F(7, 139) = 1.954$, $p = .066$, $\eta_p^2 = .090$); MF_{score}: ($F(7, 139) = .779$, $p = .606$, $\eta_p^2 = .038$); MB_{score}: ($F(7, 139) = 1.365$, $p = .225$, $\eta_p^2 = .064$); BIS-15 sum score: $F(7, 139) = 2.660$, $p = .013$, $\eta_p^2 = .118$, SURPS impulsivity subscale: $F(7, 139) = 2.518$, $p = .018$, $\eta_p^2 = .113$). We then used an elastic net analysis (Friedman et al, 2010) to select the best predictors of $Drink_{score}$ among the measures of goal-directed/habitual control and impulsivity thereby directly comparing their

respective relation to participants' drinking behavior. This analysis corroborated the findings insofar as no measure of goal-directed/habitual control was selected as predictor but both measures of impulsivity were (see Appendix A.3.4).

All behavioral analyses were repeated with all available data (n = 198) to check whether exclusion criteria influenced the results. Participants, which had previously been excluded had higher $Drink_{score}$, ADS sum score, and OCDS-G sum score, and reported lower age of 1st drink, 1st time drunk, and higher average alcohol consumption (Exact Mann-Whitney U-tests, all *p*s < .019). Nevertheless, results did not change with inclusion of these subjects.

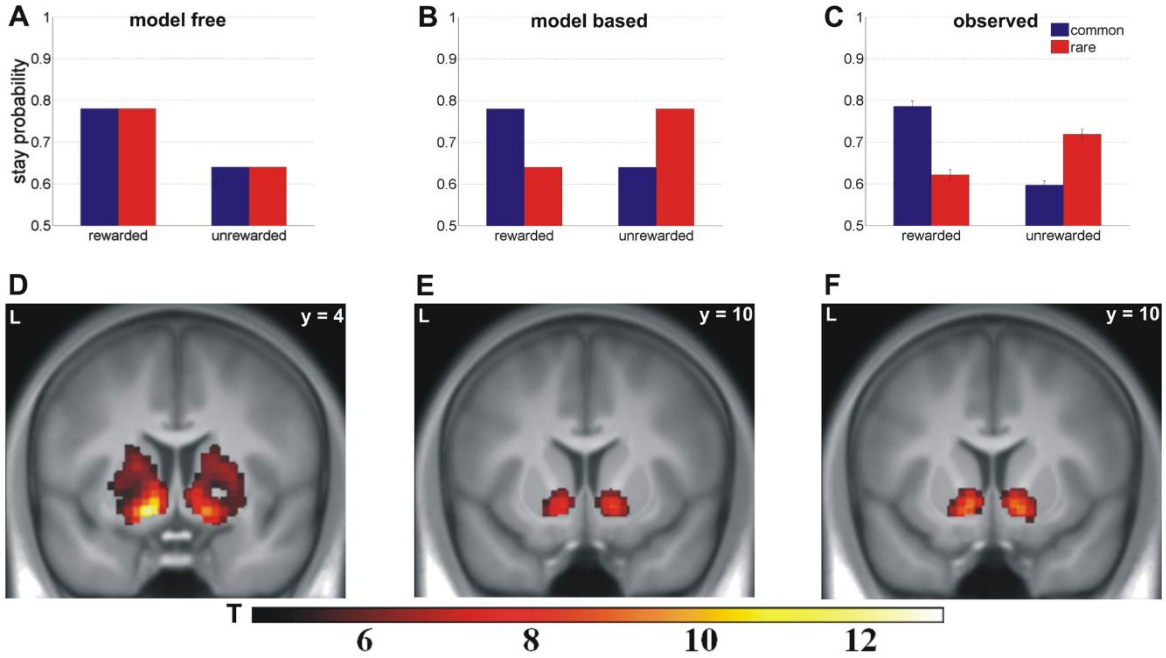

Figure 5. Upper panel: Stay probabilities in hypothetical cases of pure (a) model-free and (b) model-based control. (c) Observed stay probabilities in our sample resemble a mixture of model-free and model-based behavioral control with a tendency towards model-based control. Error bars indicate standard errors of the mean. Lower panel: Striatal BOLD correlates of (d) RPE_{MF} and (e) $RPE_{\Delta MB}$ and (f) their conjunction. Displayed at $p_{FWE} < .05$; $4.64 < t < 12.5$; whole brain analyses.

2.4.3 Functional magnetic resonance imaging results

With fMRI data, we first tested the main effects of interest, namely BOLD correlates of RPE_{MF} and $RPE_{\Delta MB}$. Separate one-sample t-tests of fMRI contrasts for RPE_{MF} and $RPE_{\Delta MB}$ were performed as ROI as well as exploratory whole-brain analyses. In addition, we tested the conjunction null hypothesis (Nichols, Brett, Andersson, Wager, & Poline, 2005) of RPE_{MF} and $RPE_{\Delta MB}$ being correlated with the BOLD responses in the same regions. BOLD responses in ventral striatum and vmPFC were associated with RPE_{MF} as well as $RPE_{\Delta MB}$ at $p_{FWE}<.05$ (Figure 5 and Table S 7-9). This replicates the finding of the original study that there are

signatures of MB evaluation in the ventral striatal BOLD response to RPEs, the "signal most associated with model free RL" (Daw et al, 2011).

Finally, we tested whether alcohol consumption is associated with neural representations of RPE_{MF} and $RPE_{\Delta MB}$. We first correlated measures of alcohol consumption with extracted mean activation in ventral striatum and vmPFC ROIs. This analysis revealed significant associations of BOLD responses to RPE_{MF} in ventral striatum with age of 1st drink (ρ = -.184, p = .026) and in vmPFC with OCDS-G sum score (ρ = .182, p = .031; Table 3). Similar to the significant correlation of γ-GT and MB_{score} on the behavioral level, these correlations did not survive Bonferroni correction for multiple comparisons (28 tests). A MANOVA with measures of drinking behavior as dependent and mean extracted ROI activation as independent variables yielded no significant results (all Fs(7,108) < .865, all ps > .537, all η_p^2s < .053). Next, exploratory whole-brain regression analyses were performed testing the relationships of RPE_{MF} and $RPE_{\Delta MB}$ with drinking measures. A negative association between BOLD responses to RPE_{MF} and age of 1st drink was revealed in a cluster in left putamen, pallidum, and insula (t(1,143) = 4.017, k = 608; Figure 4 and Table S10), which corresponds to r = .319 in the peak voxel of this cluster. This cluster also involves voxels, which are included in our mask of ventral striatum explaining the significant correlation of BOLD responses to RPE_{MF} in ventral striatum with age of 1st drink. No further measure of alcohol consumption showed an association with BOLD responses to RPE_{MF} or $RPE_{\Delta MB}$.

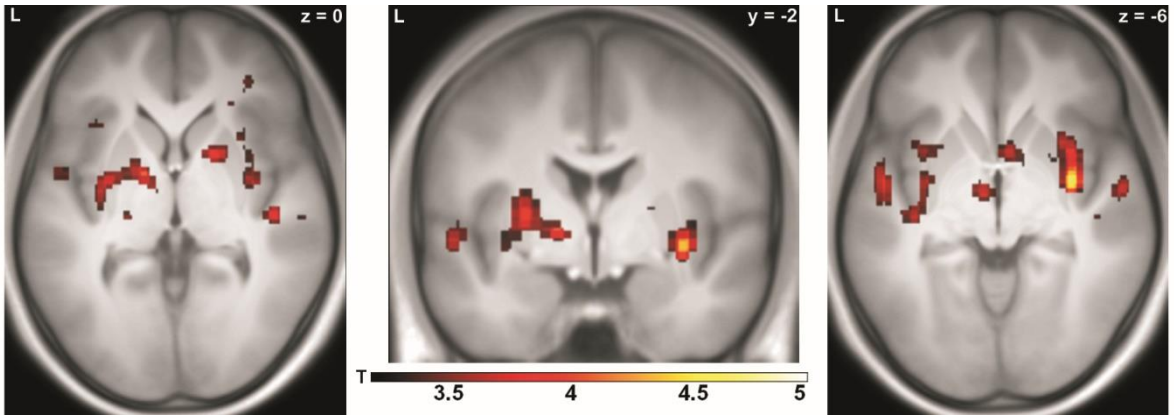

Figure 6. Negative association between BOLD response to RPE_{MF} and age of first drink. Displayed at $p_{uncorr.} < .001$; 3.15 < t < 5; whole brain analyses.

Next, we compared neural representations of RPE_{MF} and $RPE_{\Delta MB}$ between binge-drinkers and non-bingers. Exact Mann-Whitney U-tests comparing extracted mean ROI activations in RPE_{MF} and $RPE_{\Delta MB}$ contrasts in ventral striatum and vmPFC yielded no

significant differences between binge-drinkers and non-bingers (all *p*s > .414; Table S 11). Additionally, no significant differences were observed in exploratory whole-brain two-sample t-tests comparing BOLD responses to RPE_{MF} and $RPE_{\Delta MB}$, respectively, between binge-drinkers and non-bingers.

Table 3. Results of correlations between measures of alcohol consumption and behavioral measures of goal-directed/habitual control, mean extracted ROI BOLD responses to RPE_{MF} and $RPE_{\Delta MB}$ and measures of impulsivity.

	ω	MF_{score}	MB_{score}	RPE_{MF}		$RPE_{\Delta MB}$		BIS-15	SURPS
				vS	vmPFC	vS	vmPFC	SUM	IMP
$Drink_{score}$	-.067	.000	-.004	-.019	.014	-.058	-.023	.256†	.246†
Age of 1st drink	-.011	.042	.057	-.184*	-.143	-.063	-.008	-.125	-.263†
Age of 1st time drunk	.066	.052	.048	-.044	-.011	-.040	.059	-.182*	-.155*
Estimated alcohol consumption in past year (g/day)	-.070	-.071	.038	-.101	.021	-.105	-.048	.088	.116
Alcohol consumption in past year (g/drinking occasion)	-.026	-.081	.101	-.087	-.006	-.038	-.018	.133	.081
Age of 1st binge-drinking episode	.098	-.033	.019	.075	.040	.076	.047	-.156	-.126
Number of binge-drinking episodes lifetime	-.033	.038	.044	.001	.047	-.090	-.035	.232**	.179*
Alcohol consumption per binge-drinking episode (g)	-.064	.096	-.018	-.015	.048	.035	.059	.210**	.245†
ADS sum score	-.061	.007	.029	.006	.115	-.040	-.099	.211**	.298†
OCDS-G sum score	.000	-.011	.031	.088	.182*	.021	.073	.223**	.228**
AST	.015	.015	-.047	-.025	.059	-.008	-.042	.039	.165*
ALT	-.072	.061	-.080	.003	.029	.010	.030	-.018	.159*
γ-GT	-.066	-.011	-.160*	-.074	-.089	-.075	-.005	-.205**	-.092
PEth	.041	-.048	.052	-.091	-.016	-.019	.005	-.150	.005

Note: All correlations are Spearman's ρ. ADS = Alcohol Dependence Scale. ALT = alanine transaminase. AST = aspartate transaminase. BIS-15 = Barratt Impulsiveness Scale (short form) with SUM = Sum score. $Drink_{score}$ = score of drinking behavior from CIDI measures of alcohol consumption. γ-GT = gamma-glutamyl transferase. MB_{score} = score of model-based control. MF_{score} = score of model-free control. OCDS-G = Obsessive Compulsive Drinking Scale. ω = balance between model-free and model-based control. PEth = phosphatidylethanol. SURPS = Substance Use Risk Profile Scale with IMP = Impulsivity subscale. vS, ventral striatum. vmPFC, ventromedial prefrontal cortex.
* p < .05 (two-tailed); ** p < .01 (two-tailed); † p < .001 (two-tailed).

In addition, we examined the relation between measures of impulsivity and goal-directed/habitual control. There has been evidence that high impulsive subjects have a "subtle accentuation of model-free control" on a behavioral level and reduced lateral pre-/orbitofrontal model-based signals during 2-Step (Deserno, Wilbertz, et al., 2015, p. 5). In our sample, we found no significant associations between BIS-15 subscales or Sum score with λ, ω, MF_{score}, MB_{score}, as well as neural correlates of model-free and model-based control in ventral striatum and vmPFC ROIs (see Table S 6 for results of correlations) or 10mm-spheres

around the three peaks in lateral pre-/orbitofrontal cortex reported in Deserno, Wilbertz, et al. (2015).

2.5 Discussion

We investigated the association between goal-directed and habitual behavioral control during a RL task and alcohol consumption in healthy social-drinking young adults. The overall finding of our study is that there were no significant associations of measures of goal-directed or habitual control and alcohol consumption. On the behavioral level, there were no significant associations between stronger habitual or weaker goal-directed control with (1) greater alcohol consumption in general, (2) earlier onset of drinking, (3) higher average alcohol intake, (4) the presence of binge-drinking and more frequent and heavy binge-drinking events, (5) higher scores on drinking-related questionnaires, or (6) elevated levels of blood markers for liver function and alcohol consumption, except for a small correlation between model-based behavior and gamma-glutamyl transferase. On the neural level, stronger representation of model-free RPE in ventral striatum and vmPFC and weaker model-based signatures in these representations were also not significantly associated with measures of alcohol consumption. However, both ROI and exploratory whole-brain analyses revealed that participants, who reported earlier onset of drinking, showed a stronger correspondence between BOLD signals in the putamen and RPE_{MF}.

We found that on a behavioral level greater alcohol consumption at age 18 was not associated with stronger model-free habitual or weaker model-based goal-directed behavior. This suggests that favoring habitual over goal-directed control during decision making might not be a predisposing vulnerability factor for alcohol consumption per se. However, generalization is limited since we deliberately excluded subjects with rare drinking patterns amongst young men, namely complete alcohol abstinence or early alcohol dependence. We did this in order to avoid ceiling and floor effects in alcohol consumption over time, to increase the variety of possible drinking trajectories during the follow-up interval, and to not include participants who already had severe neuroadaptations due to pathological alcohol intake. Therefore, although this sample is appropriate to investigate drinking trajectories longitudinally, variance in alcohol consumption at the cross-sectional level is limited by design. This might have contributed to the lack of associations reported here. Repeating the behavioral analyses with the subjects excluded due to positive drug screenings or extreme alcohol consumption patterns increased variance in alcohol consumption but failed to alter the

results. Furthermore, despite the limited variance in drinking behavior, we did find a robust association of alcohol consumption with impulsivity. Impulsivity has often been associated with substance abuse and is thought to increase liability for addiction (Dalley, Everitt, & Robbins, 2011; Redish et al., 2008). It, therefore, seems unlikely that the current null results with respect to learning variables are due to a lack of variance in alcohol consumption. It certainly suggests that the relation between alcohol consumption and the degree of goal-directed/habitual behavioral control is negligible in comparison to the relation with impulsivity.

Another group has recently also investigated the association between goal-directed/habitual control and alcohol consumption. Investigating a large sample of 1413 participants with an internet-based online version the Two-Step task, Gillan et al. (2016) reported a negative association between AUDIT scores and model-based control. At first glance, our null finding in this regard seems to be in contrast to their result, but the association found in their sample was rather small and the sample size in our study is too low to detect associations of this magnitude. So, the results of Gillan et al.'s (2016; $|d|$=.12) and our study point to a weak association. Howsoever, web-based assessments seem to be a valuable approach to reach more participants and should be used in future studies to complement face-to-face assessments.

Two further studies used the Two-Step task in cohorts of alcohol-dependent patients after cessation of alcohol use and control groups. One of them found a significantly lower magnitude of model-based control in patients compared to control participants (Sebold et al., 2014), while the other did not (Voon et al., 2014). This discrepancy can partly be resolved: first, the difference between alcohol-dependent patients and control participants in Sebold et al. (2014) was not significant when controlling for processing speed, in which these groups differed significantly. Second, alcohol-dependent patients in Sebold et al.'s (2014) study were abstinent for about two weeks while patients in Voon et al. (2014) were abstinent from alcohol for two weeks to one year and revealed a correlation of longer duration of abstinence with more model-based control. Taken together, an imbalance in goal-directed/habitual control does not seem to increase liability for alcohol dependence substantially. If goal-directed control as measured with the Two-Step task is indeed reduced in alcohol dependent subjects, this might rather emerge during the course of prolonged, excessive alcohol use and, like other cognitive alterations, might be reversible after cessation of alcohol consumption.

As a side issue, we examined the relation between impulsivity and behavioral control during the Two-Step task and found no evidence of a behavioral or neural association. Both

impulsivity and the balance between goal-directed and habitual control have been proposed as possible vulnerability factors for addiction (Redish et al., 2008) and were hypothesized to interact (Story et al., 2014; Deserno, Wilbertz, et al., 2015). Nevertheless, our data do not support this hypothesis. However, rejecting this hypothesis in general on the basis of our results would be premature. Impulsivity is a broad, multi-facetted construct and research on finer levels of abstraction is warranted to investigate this issue further. Possibly, high motor impulsivity might lead to often favoring fast habit-like actions over slowly forward-planned actions or high delay discounting might lead to more frequent choices of temporally proximal rewards leading to faster habitization of actions due to more frequent reinforcements (Story et al., 2014).

The association of the neural representation of model-free RPEs with onset of drinking was predominantly localized in the posterior putamen, an area previously related to the representation of values learned by model-free RL (Lee et al., 2014; Wunderlich, Dayan, & Dolan, 2012), habit learning, and control of habitual behavior in healthy (Tricomi et al, 2009) and alcohol-dependent subjects (Sjoerds et al, 2013). The putamen receives extensive input from the dopaminergic midbrain nuclei (Haber and Knutson, 2010), whose output (Schultz, 1997) and BOLD response (D'Ardenne, Lohrenz, Bartley, & Montague, 2013) have been shown to represent RPEs and be causal for learning (Steinberg et al., 2013). However, this enhanced representation of model-free error signals did not translate into stronger model-free habitual behavioral control during the Two-Step task. This might indicate a compensatory mechanism by which subjects with early onset achieve the same balance between model-free and model-based control despite stronger neural representation of MF values. This could work via down-regulation of functional connectivity between posterior putamen and vmPFC, where model-free and model-based values are thought to be integrated (Lee et al, 2014). Alternatively, a change of the neural representation of model-free values might precede a measurable change of model-free behavioral control. The longitudinal design of this study will address this question. In addition, this finding will have to be replicated in future studies – just like the association of OCDS-G scores with the mean BOLD response to RPE_{MF} in vmPFC – to decrease the risk of interpreting a false positive finding.

Interestingly, acute alcohol administration has been shown to reduce goal-directed control in a devaluation task (Hogarth, Attwood, Bate, & Munafò, 2012). This could lead to habitual control taking over in acute alcohol intoxication and, thereby, increase the probability of choosing previously rewarded actions such as consuming even more alcohol. This provides a possible explanation for out-of-control binge-drinking. Hence, in terms of searching for

predictors of alcohol consumption at this age, individual volatility or state-dependence of the balance between both control systems under acute alcohol may yield better predictive properties for drinking patterns.

There are limitations of this study: First, due to our exclusion criteria this sample is not representative for the whole population of young adults. This reduces generalizability of our results. Second, we examined participants after they started drinking alcohol rather than before. Both factors preclude us from conclusively ruling out aberrant decision making as a predisposing risk factor of hazardous alcohol use, though our results strongly suggest that any present association might be negligible.

In summary, we investigated the relationship of goal-directed and habitual control and alcohol drinking behavior in young adult social drinkers. Results did not confirm our hypothesis that an imbalance between goal-directed and habitual control favoring habitual behavior was associated with greater alcohol consumption on a cross-sectional level. These results favor the view that a transition from goal-directed to habitual control as proposed by theoretical work (Everitt & Robbins, 2013) occurs during later steps on the path to an alcohol use disorder rather than being a trait marker for alcohol use per se.

Chapter 3. Study 2

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3.1 Abstract

Background: Addiction is supposedly characterized by a shift from goal-directed to habitual decision making, thus facilitating automatic drug intake. The two-step task allows distinguishing between these mechanisms by computationally modeling goal-directed and habitual behavior as model-based and model-free control. In addicted patients, decision making may also strongly depend upon drug-associated expectations. Therefore, we investigated model-based versus model-free decision making and its neural correlates as well as alcohol expectancies in alcohol-dependent patients and healthy controls and assessed treatment outcome in patients.

Methods: Ninety detoxified, medication-free, alcohol-dependent patients and 96 age- and gender-matched control subjects underwent functional magnetic resonance imaging during the two-step task. Alcohol expectancies were measured with the Alcohol Expectancy Questionnaire. Over a follow-up period of 48 weeks, 37 patients remained abstinent and 53 patients relapsed as indicated by the Alcohol Timeline Follow-back method.

Results: Patients who relapsed displayed reduced medial prefrontal cortex activation during model-based decision making. Furthermore, high alcohol expectancies were associated with low model-based control in relapsers, while the opposite was observed in abstainers and healthy control subjects. However, reduced model-based control per se was not associated with subsequent relapse.

Conclusions: These findings suggest that poor treatment outcome in alcohol dependence does not simply result from a shift from model-based to model-free control but is instead dependent on the interaction between high drug expectancies and low model-based decision making. Reduced model-based medial prefrontal cortex signatures in those who relapse point to a neural correlate of relapse risk. These observations suggest that therapeutic interventions should target subjective alcohol expectancies.

3.2 Introduction

A prominent theory in addiction research suggests that drug consumption is initially goal directed, aiming at drug-associated positive effects, then becomes habitual and eventually compulsive (Everitt & Robbins, 2005, 2016). This shift from goal-directed to habitual control has been suggested to be caused by long-lasting drug-associated changes in the medial prefrontal cortex (mPFC) and the ventral striatum which are involved in reward processing and reinforcement learning (Berridge, 2012; Heinz et al., 2004; Volkow & Li, 2004).

Behaviorally, there is good evidence for reduced goal-directed decision making facilitating habitual behavior in humans with substance use disorders (McKim, Bauer, & Boettiger, 2016), including methamphetamine (Voon et al., 2014), cocaine (Ersche et al., 2016), and alcohol dependence (Sebold et al., 2014; Sjoerds et al., 2013; but see Voon et al., 2014). Overreliance on habits at the expense of goals in AUD may be particularly pivotal during early abstinence, where patients are required to inhibit automatic patterns of alcohol intake and to develop alternative coping strategies (Tiffany & Conklin, 2000; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). Neuroimaging studies implicate a crucial role for the mPFC and the ventral striatum for the balance between goal-directed and habitual control (Alexander & Brown, 2011; S. de Wit et al., 2009; Killcross & Coutureau, 2003; O'Doherty, 2011; Ostlund & Balleine, 2005), craving (Goldstein & Volkow, 2011), and relapse in AUD (Beck et al., 2012; Charlet et al., 2014; Grüsser et al., 2004). Moreover, in animals, there is evidence that habits (e.g., automatic action tendencies) precede relapse-like behavior (Barker, Torregrossa, & Taylor, 2012; Flagel, Waselus, Clinton, Watson, & Akil, 2014; Katner, Magalong, & Weiss, 1999).

However, habit formation is not only a deficit: it is a fundamental and adaptive ability, and using habits facilitates decision making whenever cognitive resources are limited (Otto, Gershman, Markman, & Daw, 2013) or action sequences are too complex to mentally compute them (Huys et al., 2012). In AUD, specific habits may be altered and induce alcohol craving, seeking, and intake. Besides habit formation, positive alcohol expectancies as assessed by the Alcohol Expectancy Questionnaire (AEQ; Brown, 1985; Brown, Goldman, Inn, & Anderson, 1980) have been associated with current (Leigh, 1989) and future (Goldman & Darkes, 2004; Reese, Chassin, & Molina, 1994) alcohol consumption. Explicit, self-report measures of alcohol expectancies reflect the specific expectations of the reinforcing effects of alcohol and are associated with prefrontal cortex activity and structure (Anderson, Schweinsburg, Paulus, Brown, & Tapert, 2005; Deckel, Hesselbrock, & Bauer, 1995;

Gundersen, Specht, Grüner, Ersland, & Hugdahl, 2008; Ide et al., 2014; Wiers et al., 2007). One study in humans has demonstrated that acute expectation of alcohol induced by presenting alcohol beverages impairs goal-directed regulation of drug-seeking behavior in social drinkers (Hogarth, Field, & Rose, 2013), which parallels animal findings (Ostlund, Maidment, & Balleine, 2010). Such acute expectation of alcohol may be particularly strong in subjects who have generally positive expectancies regarding the effects of alcohol consumption. Indeed, subjects who report greater positive, arousing, and social alcohol expectancies show increased appetitive responses toward alcohol cues (Drobes, Carter, & Goldman, 2009). However, it is yet unclear how this association relates to real-life drinking behavior and treatment outcome in AUD.

We recruited recently detoxified alcohol-dependent patients who expressed a desire to remain abstinent. We asked whether a tendency for positive alcohol expectancies interacts with model-based control and its neurobiological correlates in predicting treatment outcome.

3.3 Methods and materials

3.3.1 Participants

All data were collected as part of the Learning and Alcohol Dependence study, a bicentric German study hosted at Universitätsklinikum Dresden/Technische Universität Dresden and Charité–Universitätsmedizin Berlin. Two hundred two subjects (106 AUD patients, 96 control participants) completed the Two-Step task (Daw et al., 2011) to disentangle habitual from goal-directed decision making and the brief German version of the AEQ (Brown, 1985). Patients fulfilled diagnostic criteria for alcohol dependence according to ICD-10 and DSM-IV-TR (Saß et al., 2003) for a minimum of 3 years. Healthy control subjects were carefully matched for age, gender, education, and smoking. Exclusion criteria for all subjects were left-handedness [Edinburgh Handedness Inventory <50 (Oldfield, 1971)], a history of current or past substance use disorder (except nicotine dependence in control participants and alcohol and nicotine dependence in AUD patients), other major psychiatric disorder [as assessed with the computer-based CIDI (Jacobi et al., 2013; Wittchen & Pfister, 1997)], or neurological disease. No subjects were using psychotropic medications that were known to interact with the central nervous system for at least four half-lives (including illegal drugs and detoxification treatment tested by a drug urine test). Study participation of the patients took place shortly after detoxification (Table 4). Participants gave written informed consent. Ethical approval for the study was obtained from both sites (Universitätsklinikum

Dresden/Technische Universität Dresden, EK 228072012; Charité–Universitätsmedizin Berlin, EA 1/157/11), and procedures were in accordance with the Declaration of Helsinki.

3.3.2 Procedure

Participants were seen twice for investigation. In the first assessment, participants completed the CIDI, a neuropsychological test battery, and additional questionnaires (Table 4). Subjects completed the German version of the AEQ at this time (Brown, 1985). On the second appointment, which took place shortly after the first appointment (mean ± SD, 7.0 ± 12.2 days), subjects performed the Two-Step task (Daw et al., 2011) along with another learning task (Garbusow et al., 2014). The two-step task was programmed using Matlab software (The MathWorks, Inc., Natick, MA) with the Psychophysics Toolbox (Brainard, 1997) and was performed while undergoing fMRI. All participants had negative alcohol breath tests and patients were free of significant withdrawal symptoms [Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA) score ≤3 (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989)]. Participants received compensation of 10 € an hour plus a financial bonus contingent on their performance. Blood samples for analysis of ALT, AST, γ-GT, and PEth were collected.

3.3.3 Alcohol Expectancy Questionnaire

The brief German version of the AEQ includes 19 items. Each item describes anticipated reinforcing effects of alcohol. Items include statements such as “Alcohol generally has powerful positive effects on people (e.g., makes a person feel good or happy)” or “Alcohol helps a person to relax (e.g., feel less tense, can keep a person’s mind off of mistakes at work).”

Subjects are asked to agree or disagree with each item. Disagreement and agreement of each item are coded as 1 and 2, respectively, resulting in a potential sum score between 19 and 38, for low to high expected reinforcement, respectively.

3.3.4 Task

Each participant performed 201 trials of the Two-Step task (Figure 7A, see section 2.3.2 for detailed task description). This task enables the analysis of model-based (goal-directed)

and model-free (habitual) decisions on a trial-by-trial level, because both decision strategies make distinct predictions on choice behavior (Figure 7B).

3.3.5 Magnetic Resonance Imaging

fMRI was performed using a 3T Siemens Trio scanner (Siemens, Erlangen, Germany) with a 12-channel head coil. For fMRI, we used a T2-weighted echo planar imaging sequence with the following parameters: TR = 2410 ms, TE = 25 ms, 80° flip angle, 3 × 3 × 2 mm^3 voxel size, and a 192 × 192 mm^2 field of view. One volume comprised 42 transverse slices in descending order, oriented 25° to the anteroposterior commissure line. We additionally acquired a structural T1-weighted MPRAGE image (TR = 1900 ms, TE = 2.52 ms, 9° flip angle, 1 × 1 × 1 mm^3 voxel size, 256 × 256 mm^2 field of view).

3.3.6 Follow-up procedure

After study participation, alcohol-dependent patients were regularly contacted for personal (after 4, 8, 12, 24, and 48 weeks) and telephone (after 6, 10, 18, and 36 weeks) assessments over a period of 1 year. At each contact, we assessed daily alcohol intake amount using the Alcohol Timeline Followback method (Sobell & Sobell, 1992), with relapse defined as consumption of 60/48 g (male/female) of alcohol on any occasion. Personal assessment included alcohol breath tests to validate self-reports. During the follow-up period, we lost 16 patients (15%). In two cases, we only had relapse reports from close relatives, which we accepted for classification. Altogether, 53 patients (59%) relapsed during the follow-up period, whereas 37 (41%) remained abstinent. Demographic and clinical characteristics of this sample are shown in Table 4.

3.3.7 Data analysis

We investigated two questions: 1) whether the balance between model-free and model-based control was different between control participants and detoxified alcohol-dependent patients who remained abstinent (abstainers) and who subsequently relapsed (relapsers), and 2) whether the balance between model-free and model-based control moderated the effect of alcohol expectancies on drinking behavior. As previous studies have overwhelmingly suggested that the two-step task has power to detect variations in the goal-directed but not the habitual system (Doll, Bath, Daw, & Frank, 2016; Gillan et al., 2015; Sebold et al., 2014;

Voon et al., 2014), we focused on individual differences in model-based control in all analyses. We tested assumptions for all statistical analyses and computed nonparametric tests when necessary.

3.3.7.1 Task-related group differences

To derive individual measurements of model-based control from behavior of the two-step task, we focused on first-stage choices because model-free versus model-based decision making is differentially affected by reward and transition from the previous trial (Daw et al., 2011) (Figure 7B). We calculated individual model-based scores, as done previously (Sebold et al., 2014), which reflect the interaction between transition frequency and reward of the previous trial (% reward common + % unrewarded rare – % rewarded rare – % unrewarded common). Model 1A involved a multinomial logistic regression analysis (multinom function from the nnet package [version 7.3-8] in R software [available at https://www.R-project.org]) to test whether group (dummy coded with three levels: control participants, abstainers, and relapsers) was predicted from model-based scores.

The raw data analysis provides a direct measurement of model-free and model-based behavior. However, it only considers trial-by-trial repetition effects. Computational models allow more comprehensive assessments, examining longer behavioral trends. Therefore, we fitted a hybrid model as previously described (Daw et al., 2011; Deserno, Huys, et al., 2015; Deserno, Wilbertz, et al., 2015) to the behavior and estimated parameters for each subject. We used an expectation maximization algorithm to find maximum a posteriori estimates. During the fitting procedure, all subjects (control participants, abstainers, relapsers) were treated as one group.

The hybrid model contains seven parameters, of which the parameter ω is of major interest because it determines the balance between model-free (ω = 0) and model-based (ω = 1) control. Crucially, this seven-parameter hybrid model was the best-fitting model for all groups (Figure S 3). The estimation of the parameter ω relies on the fact that subjects concurrently use model-free and model-based strategies. We excluded subjects who did not use this hybrid model as indicated by the individual log-likelihoods that did not fit better than chance (see Appendix B.1.1; n in analyses = 143). Model 1B then mirrored the analysis of the first-step repetition probabilities: again, we performed a multinomial logistic regression analysis to test whether ω was predictive of group membership (control participants, abstainers, and relapsers). In line with Voon et al. (2014), we compared all other model parameters between groups (Table S 12).

3.3.7.2 Interaction between alcohol expectancies and model-based control

Our second hypothesis was that model-based scores would moderate the effect of alcohol expectancies on group. Model 2A tested this using multinomial logistic regression where we additionally allowed for interaction between AEQ scores and model-based control to predict group. To elucidate the direction of our effects, we computed post hoc Spearman correlations between AEQ scores and model-based control within all groups. For illustrative purposes and further analyses, we assigned participants to high versus low alcohol expectancy groups using median splits of the AEQ (control participants Mdn = 25; AUD patients Mdn = 35). We compared models 1A and 2A with respect to model fit. To assess the predictive capacity of the winning model, we additionally performed a cross-validation approach (stratified 10-fold cross-validation with class balancing during training). Finally, model 2B replicated the above analysis using the computational parameter ω. We compensated for the reduced power caused by the removal of poorly fit subjects (see Appendix B.1.1) by using categorical AEQ information. Again, we compared models 1B and 2B with respect to model fit. Post hoc analyses were performed, comparing ω between individuals with high and low alcohol expectancies within each group using Kruskal–Wallis tests. To evaluate whether AEQ scores were related to a motivational aspect of alcohol intake, we correlated AEQ scores with sum scores of the Drinking Motives Questionnaire (Kuntsche, Knibbe, Gmel, & Engels, 2006), which measures motives of alcohol intake (Gmel, Labhart, Fallu, & Kuntsche, 2012).

3.3.8 fMRI analysis

Preprocessing details of the fMRI data can be found in the Supplement. All first-level analyses were based on 116 subjects (60 control participants, 21 abstainers, and 35 relapsers; see Figure S 4 for dropout details). In line with the hypothesis that relapse in AD is characterized by a shift away from model-based control, the aim of the statistical analysis of the fMRI data was to elucidate whether relapsers would show decreased model-based neural signatures in brain areas associated with the computation of these learning signals (Daw et al., 2011; Deserno, Huys, et al., 2015; Deserno, Wilbertz, et al., 2015).

First-level analyses were conducted as previously described (Daw et al., 2011; Deserno, Huys, et al., 2015; Deserno, Wilbertz, et al., 2015; Appendix A.2.1, Appendix B.4). Briefly, we derived individual RPE_{MF} and RPE_{MB} trajectories from the computational model under the assumption of pure model-free (ω = 0) versus full model-based control (ω = 1), respectively. In line with Daw et al. (2011), we used means across all groups for all parameters to compute

prediction errors. Next, we used RPE_{MF} as a parametric regressor in the first-level analyses and added a second regressor—$RPE_{\Delta MB}$, the difference between RPE_{MF} and RPE_{MB}—to explain variance in the blood oxygen level–dependent signal uniquely related to model-based prediction errors. At the second level, contrast images for RPE_{MF} and $RPE_{\Delta MB}$ were taken to a random effects analysis. Site (Berlin vs. Dresden) was added as a covariate of no interest. For correction of multiple comparisons, familywise error (FWE) correction with $p = .05$ at the peak level was applied for whole brain analyses. Group comparisons in the mPFC and the ventral striatum — both areas with a pivotal role in coding RPE_{MF} and $RPE_{\Delta MB}$ signals (Daw et al., 2011; Deserno, Huys, et al., 2015; Deserno, Wilbertz, et al., 2015; Gläscher et al., 2010; Lee et al., 2014) — were performed using small volume correction (SVC) with a mask containing all voxels showing a significant effect for RPE_{MF} and $RPE_{\Delta MB}$ (conjunction at $p_{uncorr.} < .001$) combining all three groups.

There is evidence for pronounced structural alterations in relapsers compared to abstainers in the mPFC, a region of interest (Beck et al., 2012; Charlet et al., 2014; Durazzo et al., 2011). We conducted voxel-based morphometry (Ashburner & Friston, 2000) and added gray matter density as a nuisance variable in our fMRI analysis to control for morphometric alterations in the fMRI analyses (Table S 13).

To mirror the behavioral analyses, we additionally tested whether model-based neural signatures would differently correlate with AEQ scores between groups. As we had assumed that the interaction between model-based neural correlates and alcohol expectancies plays a role in the predefined regions (right/left ventral striatum and mPFC), we extracted average model-based cluster activity of these regions. Mirroring our behavioral analyses, we performed three subsequent multinomial regressions with group as dependent variable and tested for the interaction between AEQ scores and the respective cluster values.

3.4 Results

3.4.1 Sample characteristics

Compared to control participants, abstainers and relapsers reported significantly higher symptoms in almost all clinical characteristics, increased deficits in neuropsychological testing, and increased blood parameters related to alcohol consumption (Table 4).

Table 4. Sample characteristics of the final sample.

Variable	Group									*p*-values for test statistic			
	Control participants (n=96)			Abstainers (n=37)			Relapsers (n=53)			Main effect group	Controls vs. Abstainers	Abstainers vs. Relapsers	Controls vs Relapsers
Gender	♀: 16; ♂: 80			♀: 7; ♂:30			♀: 6; ♂: 47			.56[b]	.8[b]	.37[b]	.47[b]
Site	Berlin: 56; Dresden: 40			Berlin: 24; Dresden: 13			Berlin: 28; Dresden: 25			.52[b]	.56[b]	.28[b]	.61[b]
	M	SD	NA	M	SD	NA	M	SD	NA	F	T	T	T
Demographical variables													
Years of school education	11.9	1.5	2	10.8	1.5	2	10.6	3.5	2	<.05[c]	.20[c]	.61[c]	<.05[c]
Age	43.6	10.9	0	45.7	12.0	0	45.2	9.9	0	.52[a]	.36[a]	.82[a]	.38[a]
Net income in €	1201	686	22	1150	741	0	1013	621	5	.22[c]	.61[c]	.38[c]	.08[c]
Proportion of smokers	65%	-	0	75%	-	0	75%	-	0	.33[b]	.45[b]	>.99[b]	.45[b]
Duration of abstinence at fMRI	66.5	280.9	0	21.4	11.6	0	22.3	12.4	0	<.0001[c]	<.0001[c]	.80[c]	<.0001[c]
Clinical characteristic													
Number of detoxifications	-	-	-	2.13	2.06	0	4.75	5.03	0	<.05[c]	-	<.05	-
AEQ	25.7	4.6	0	31.7	4.4	0	32.8	3.9	0	<.0001[c]	<.0001[c]	.20[c]	<.0001[c]
HADS-D	1.9	2.3	1	3.9	3.9	0	4.2	3.7	0	<.0001[c]	<.001[c]	.67[c]	<.0001[c]
OCDS-G	2.7	2.8	1	10.3	8.2	1	12.9	8.4	3	<.0001[c]	<.0001[c]	.10[c]	<.0001[c]
DMQ-R	29	7	3	44	11	1	48	14	1	<.0001[c]	<.0001[c]	.36[c]	<.0001[c]
Time to relapse in days	-	-	-	-	-	-	87.1	80.0	4	-	-	-	-
Neuropsychological testing													
MWT-B	28.3	4.6	3	28.6	4.3	0	28.2	4.8	1	.90[c]	.87[c]	.73[c]	.96[c]
DSST	10.7	3.12	0	9.9	2.6	1	9.1	2.9	0	<.01[a]	.11[a]	.26[a]	<.01[a]
DSbw	7.5	2.04	0	6.62	1.91	0	6.54	1.89	0	<.01[a]	<.05[a]	.86[a]	<.01[a]
Blood markers													
AST(µKat/l)	0.45	0.17	28	0.69	0.53	5	0.71	0.52	11	<.001[c]	<.05[c]	.68[c]	<.001[c]
ALT (µKat/l)	0.43	0.19	28	0.88	0.73	5	1.08	2.16	11	<.001[c]	<.01[c]	.94[c]	<.001[c]
γ-GT (µKat/l)	0.54	0.67	28	3.33	6.71	5	1.51	1.38	11	<.0001[c]	<.0001[c]	.91[c]	<.0001[c]
PEth (ng/ml)	203.24	359.68	16	447.85	349.13	16	806.15	736.83	31	<.0001[c]	<.0001[c]	.14[c]	<.0001[c]

Note: AEQ = Alcohol Expectancy Questionnaire. ALT = alanine transaminase. AST = aspartate transaminase. DMQ-R = Drinking Motives Questionnaire, revised version. DSbw = digit span backwards. DSST = Digit Symbol Substitution Test. γ-GT = gamma-glutamyl transferase. HADS-D = Hospital Anxiety and Depression Scale, Depression subscale. M: mean. MWT-B = Mehrfachwahl-Wortschatz Test, version B. OCDS-G = Obsessive-Compulsive Drinking Scale. PEth: phosphatidylethanol. SD: standard deviation.

[a] p-value of linear model (LM) with group as predictor, or p-value of respective contrast.

[b] p-value of Chi-Square Test.

[c] p-value of Kruskal-Wallis Rank Sum Test with group as predictor or Wilcoxon Rank Sum Test for respective contrast.

Matching of control participants and alcohol-dependent patients was successful in all variables of interest (gender, school education, smoking status, and age). At baseline, there were no significant differences between abstainers and relapsers, except that the patients in the relapse group reported a larger number of previous detoxifications.

3.4.2 Task-related group differences

Model-based control per se did not predict group membership of control participants, abstainers, or relapsers (model 1A; R^2_{McF} = .003, p = .55; Figure 7C). The computational analysis confirmed these results. The parameter ω was not associated with group (model 1B; R^2_{McF} = .003, p = .60).

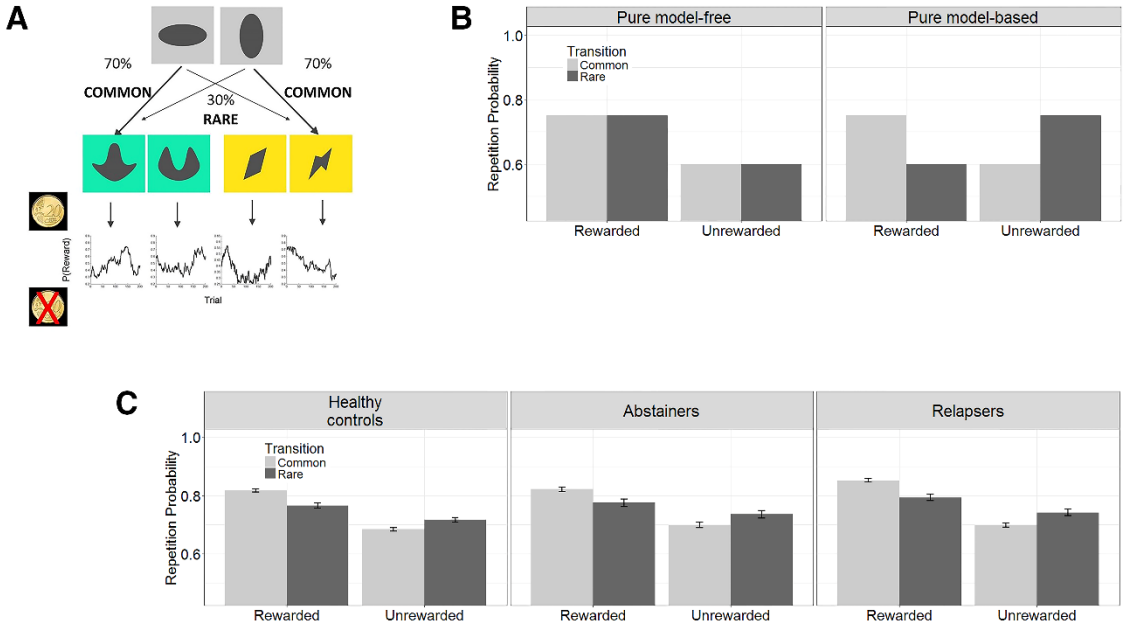

Figure 7. (A) Design of the Two-Step task. (B) Exemplary model-free and model-based response patterns. While pure model-free decisions only depend on the reward in previous trials, model-based decisions take transition frequencies from first to second stage into account. (C) Real response pattern as a function of group. All three groups showed a mixture of model-free and model-based decision making. Groups did not differ significantly regarding their model-free or model-based choice pattern.

3.4.3 Interaction between alcohol expectancies and model-based control

However, model-based control and alcohol expectancies interacted in predicting group membership (model 2A; R^2_{McF} = .23, p = .01). This interaction was significantly different between relapsers and control participants (p < .01) and trendwise different between relapsers and abstainers (p = .06). Post hoc analyses using Spearman correlation to associate AEQ

scores with model-based control indicated a positive association in control participants (ρ = .20, p = .04) which was absent in abstainers (p = .36, Figure 2A) and negative in relapsers (ρ = −.30, p = .03). Model comparisons between models 1A and 2A indicated that model 2A, which included the interaction between the model-based term and AEQ scores to predict group membership, outperformed model 1A, which included only the model-based term (χ^2 = 87.1, p < .001). To ensure the robustness of our analysis in a predictive classification scheme, we ran the logistic regression model in a cross-validated procedure. The regression model correctly predicted group membership with an area under the curve of 0.77 (chance level: 0.5; $p < 10^{-4}$ based on a permutation test with 10,000 label permutations), corroborating the significant predictive capacity of model 2A.

Similar to our raw data analysis, model 2B indicated a significant interaction between ω and AEQ scores (R^2_{McF} = .12, p = .01), which was significantly different between relapsers and control participants (β = 1.48, p < .01) and did not reach significance between relapsers and abstainers (β = 1.8, p = .1). Again, model 2B outperformed model 1B, which only included the parameter ω (χ^2 = 10.2, p = .03).

Post hoc analyses comparing high and low AEQ individuals revealed a positive association between AEQ scores and ω in control participants (p < .01), but no significant association between AEQ and ω in abstainers (p = .51) and a trend toward negative association between AEQ and ω in relapsers (p = .05, Figure 8C). Adding site as a potential covariate did not change any of these results. Repeating our analyses with time to relapse as dependent variable did not reach significance (Appendix B.8).

Among all subjects, AEQ scores were positively correlated with a variety of drinking motives (Figure S 5-6).

3.4.4 fMRI results

Across all groups and in line with previous work (Daw et al., 2011; Deserno, Huys, et al., 2015; Deserno, Wilbertz, et al., 2015), the conjunction between RPE_{MF} and $RPE_{\Delta MB}$ reached significance in the bilateral ventral striatrum (t = 6.38, x = 12, y = 12, z = –8 and t = 6.27, x = –16, y = 8, z = –10, p_{FWE} < .001) and the mPFC (t = 4.85, x = –8, y = 32, z = –8, p_{FWE} < .05) (Figure 9A; Table S 14). Within these regions, we found a significant correlation between neural model-based signatures (average cluster activation) and model-based scores in control participants (right ventral striatum: ρ = .29, p = .02; mPFC: ρ = .27, p = .03; Figure 9B).

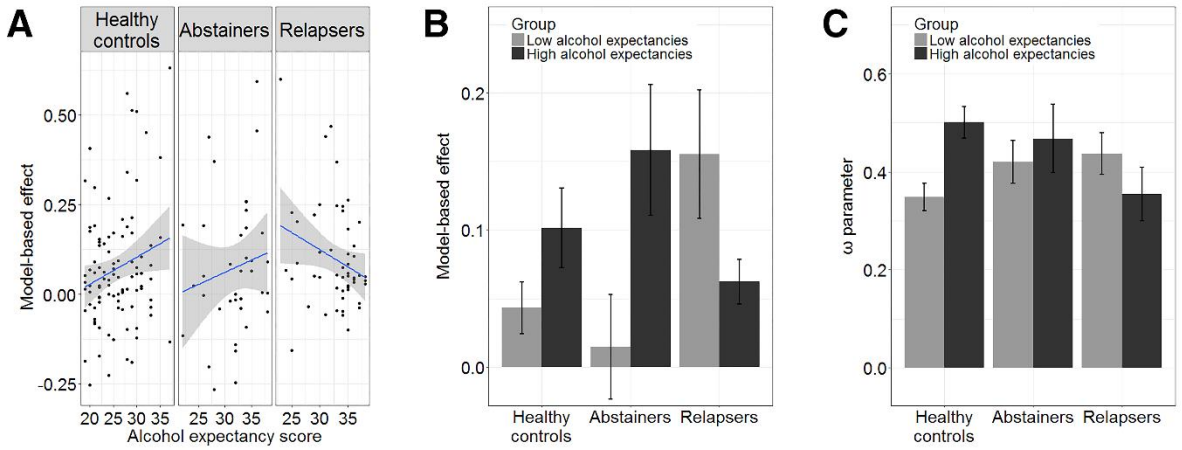

Figure 8. (A, B) Model-based strategy usage as a function of alcohol expectancies. Subsequent relapsers showed a negative relationship between alcohol expectancies and model-based control. This negative association was not apparent in the abstaining patients and positive in the healthy control subjects. (C) The relationship between u, which indicates the balance between model-based and model-free decision making, and positive alcohol expectancies. Again, whereas healthy control subjects showed a positive association between u and alcohol expectancies, this association was negative in relapsers and absent in abstaining patients.

With regard to group comparisons, control participants did not differ from alcohol-dependent patients. However, with regard to treatment outcome, we observed significantly lower model-based prediction error signals ($RPE_{\Delta MB}$) in the mPFC for relapsers compared to abstainers and control participants (t = 3.9; x = –16, y = 42, z = –8, p_{FWE_SVC} = .026; Figure 9C). Post hoc analyses, for which we extracted estimates from the peak voxel in the mPFC and compared activation between groups, indicated significantly higher activation in control participants compared to relapsers (t = 3.47, p < .001) and trendwise higher activation in control participants compared to abstainers (t = 1.74, p = .08). Abstainers and relapsers did not differ (p = .10). Crucially, adding individual gray matter densities of the mPFC did not change these results (p_{FWE_SVC} = .024), suggesting that reduced neural signatures of model-based RPEs in relapsers were not caused by gray matter atrophy (Table S 13).

Model-free neural signatures did not differ between groups (Figure S 7).

Mirroring our behavioral analyses, we also examined whether AEQ scores interacted with neural correlates of model-based control in predicting group. However, the interaction between neural correlates of model-based control and AEQ scores was not significantly different between groups, neither in the left (relapsers vs. abstainers, p = .06; relapsers vs. control participants, p = .32) or right ventral striatum (relapsers vs. abstainers, p = .10; relapsers vs. control participants, p = .54) nor in the mPFC (relapsers vs. abstainers, p = .60; relapsers vs. control participants, p = .21).

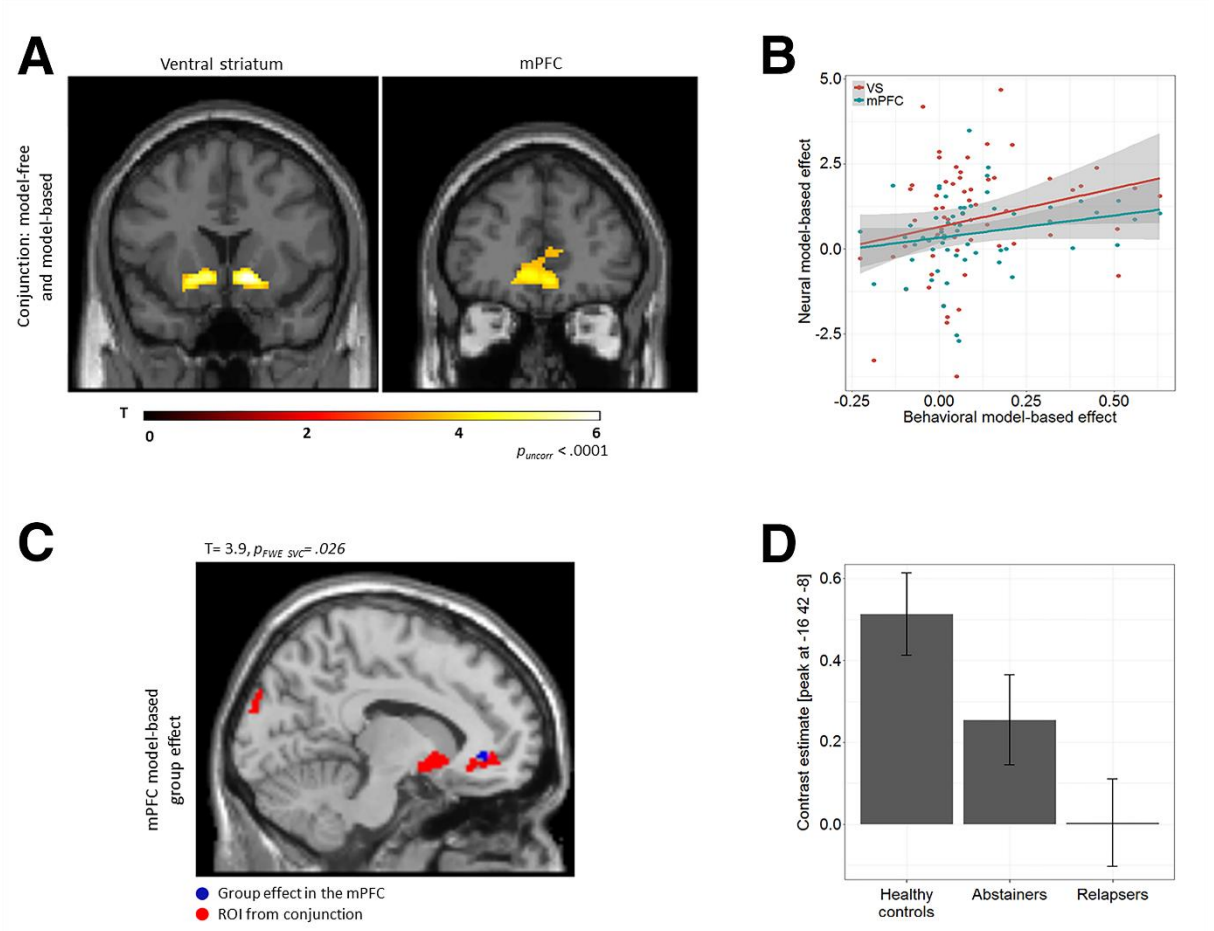

Figure 9. (A) Conjunction. Across all three groups, we found a significant coding of model-free prediction errors and additional model-based prediction errors in the ventral striatum (VS) and the medial prefrontal cortex (mPFC) (conjunction displayed at $p_{uncorr.} < .0001$). These regions were also the only ones that reached significance at a more conservative threshold ($p_{FWE} < .05$). (B) Association between neural and behavioral model-based effects. (C) Group effects. A region of the mPFC showed reduced model-based signatures for relapsers compared to abstainers and healthy control subjects. This effect survived small volume correction for the main effects of the above reported conjunction ($p_{FWE} < .026$) (panel A). Model-free signatures were not statistically different between groups. ROI = region of interest.

3.5 Discussion

The main findings of our study are 1) a reduction in mPFC activation during model-based behavior in relapsers and that 2) an interaction between alcohol expectancies and goal-directed control distinguishes relapsers from abstainers and control participants. Reductions in goal-directed behavior per se were not significantly associated with AUD or relapse. Instead, relapsers had high alcohol expectancies in association with low goal-directed behavior and vice versa, suggesting that the interaction between alcohol expectancies and habitual drug intake characterizes subjects with low treatment outcome.

Replicating previous studies (Cooper, Frone, Russell, & Mudar, 1995; Wiers et al., 2007), alcohol expectancies were correlated with drinking motives, suggesting that high alcohol expectancies reflect a motivation to consume alcohol. In abstainers and control

participants, high alcohol expectancies were associated with stronger model-based control, which might help these subjects to use alcohol within a framework of self-determined values and goals. Conversely, relapsers with relatively high model-based control had low alcohol expectancies and may accordingly underestimate the effect of even low doses of alcohol to achieve a certain desired state of intoxication, whereas reductions in model-based control might facilitate excessive alcohol intake when general alcohol expectancies are high. Indeed, Hogarth et al. (2013) observed that acute expectation of alcohol can temporarily interfere with goal-directed control. Our data add to this line of arguments and suggest that beyond momentary effects of alcohol expectations, a tendency to expect positive and reinforcing alcohol effects is particularly dangerous when combined with habitual or compulsive patterns of alcohol intake (Everitt & Robbins, 2005, 2016). Our findings differed to some degree from a study in cocaine and polysubstance abusers, where decreased goal-directed control was found (Ersche et al., 2016; McKim, Bauer, et al., 2016). Likewise, Voon et al. (2014) observed such reduction in methamphetamine abusers but not alcohol-dependent patients, whereas a study from our own laboratory in an independent sample suggested that AUD was related to reductions in goal-directed control (Sebold et al., 2014).

Consumption of legal drugs (e.g., alcohol) is sensitive to social traditions, including expected alcohol effects on personal well-being and social interactions. Such influences may be particularly important for subjects with AUD. We also observed that functional correlates of model-based behavior in the mPFC were reduced in relapsers compared to abstainers and control participants, while at the behavioral level model-based decision making differed only between these groups when alcohol expectancies were taken into consideration. This suggests that neural activation patterns during cognitive tasks provide a valuable tool for predicting treatment outcomes (Gowin, Ball, Wittmann, Tapert, & Paulus, 2015) independent of alcohol expectancies. Two other studies have associated blunted mPFC activation with reduced goal-directed control and flexible decision making in AUD (Reiter et al., 2016; Sjoerds et al., 2013). The mPFC plays a key role in alcohol-associated behavior, including cue-induced craving in animals (Koya et al., 2009; Park et al., 2002) and humans (Childress et al., 1999; Heinz et al., 2005). Further evidence for a role of the mPFC in relapse comes from animal studies, where drug-associated mPFC activity has been shown to provoke relapse to diamorphine (Bossert et al., 2011). In humans, relapse in AUD has been associated with enhanced cue-related activity in the mPFC (Beck et al., 2012; Grüsser et al., 2004). These findings suggest that impaired mPFC function and a potential bias toward cue-induced

functional activation in association with drug craving characterizes relapse across substance use disorders.

There are several limitations that need to be addressed. First, our sample size, although comparatively large, includes only a limited number of abstainers (n = 21) available for imaging, and effect sizes for the behavioral data were only moderate. Second, rodent studies have demonstrated a bias toward habitual control after chronic alcohol reward (Doll et al., 2016; Sobell & Sobell, 1992; Sullivan et al., 1989). The task here, however, used only monetary, nondrug rewards (Ersche et al., 2016; Sebold et al., 2014; Sjoerds et al., 2013; Voon et al., 2014) and no alcohol cues. To what extent habitization of monetary outcomes captures the processes induced by alcohol is unclear, but ethical concerns limit the use of alcohol in detoxified subjects with AUD.

Third, alcohol expectancies, although reflecting a trait rather than a state marker of motivation (Aas, Leigh, Anderssen, & Jakobsen, 1998; Duka, Tasker, & Stephens, 1998), are directed at consuming alcohol and are thus outcome oriented. In our study, this motivational trait was associated with low model-based control in relapsers. We do not know whether individual relapses were triggered by acute expectation of alcohol, e.g. elicited by alcohol cues. However, acute expectation of alcohol could not be tested as all subjects were motivated to remain abstinent. Additional studies in individuals with low substance use (e.g., heavy drinkers without dependence) may help to identify the effects of acute alcohol expectations on decision making.

Fourth, relapsers had gone through significantly more previous detoxifications compared to abstainers, which may contribute to neurobiological alterations associated with further and even more excessive alcohol intake, as indicated by animal experiments (Spanagel & Hölter, 1999; Vengeliene, Bilbao, & Spanagel, 2014; Vengeliene, Celerier, Chaskiel, Penzo, & Spanagel, 2009). However, model-based neural correlates in the mPFC were not associated with previous detoxifications in the patient group (Appendix B.9). Finally, our study cannot disentangle preexisting conditions from alcohol-induced changes [e.g., on dopaminergic neurotransmission and its effect on goal-directed correlates (Deserno, Huys, et al., 2015)]; therefore, further studies employing longitudinal designs are required.

In conclusion, decreased model-based control may predict relapse only in patients with high alcohol expectancies. This study further specifies the theory of goals and habits in AUD and suggests a pivotal role of alcohol expectancies, which can easily be assessed in clinical settings. Our study showed how the computational mechanism underlying goal-directed control and its neurobiological correlate (reduced mPFC activation) are associated with poor

treatment outcome. The interaction between alcohol expectancies and drug taking habits points to potential therapeutic interventions that aim to increase goal-directed control (such as motivational interviewing) and alter the anticipated outcomes of alcohol use.

Chapter 4. Study 3

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4.1 Abstract

Background: Impulsive decision making relates to problematic substance use. Specifically, altered delay discounting has been suggested as a behavioral marker for addiction, while other relevant facets of choice impulsivity such as probability discounting or loss aversion are clearly understudied.

Methods: Two studies were performed collecting behavioral data on choice impulsivity with a value-based decision-making battery providing estimates of delay discounting, probability discounting for gains and losses, and loss aversion. *Study 3.1)* In a sample of 198 male 18-year-old social drinkers, we analyzed impulsive choice behavior and its association with alcohol consumption and self-report measures of substance use related personality traits on a cross-sectional level. Additionally, the predictive value of baseline choice behavior for the trajectories of alcohol consumption over a 12-month follow-up period was evaluated. *Study 3.2)* Behavioral data on choice impulsivity was collected for 114 detoxified patients with alcohol use disorder (AUD) and 98 control participants. We analyzed group differences at baseline and assessed the predictive value of choice impulsivity for relapse to heavy alcohol use in patients during a follow-up period of 48 weeks.

Results: *Study 3.1)* Only delay discounting was associated with baseline alcohol use, but no measure of choice impulsivity predicted the drinking trajectories over the following 12 months. *Study 3.2)* Compared to the control group, AUD patients showed higher delay discounting, lower risk aversion regarding probabilistic gains, lower risk seeking regarding probabilistic losses, and lower loss aversion facing mixed prospects. Further, shallow discounting of probabilistic losses at baseline was predictive for relapse in patients.

Conclusions: All four domains of impulsive decision making were considerably altered in AUD patients though mostly not related to alcohol use in young-adult social drinkers. This suggests that these facets of impulsive behavior may develop as consequences of chronic

alcohol consumption. Furthermore, discounting of probabilistic losses might prove valuable in identifying patients vulnerable for relapse.

4.2 Introduction

Biased decision making is fundamental to several neuropsychiatric disorders such as SUDs (Redish et al., 2008), eating disorders (Amlung, Petker, Jackson, Balodis, & MacKillop, 2016), and attention-deficit/hyperactivity disorder (Jackson & MacKillop, 2016), and also to self-regulation and health behavior in general (Story et al., 2014). In SUDs, drug consumption can be considered an impulsive choice for a highly probable immediate outcome, e.g. hedonic experience, peer bonding, pain or stress relief, on the possible expense of long-term health, social, and financial benefits. Choice impulsivity includes two aspects of the definition of impulsivity: lack of planning and lack of regard for future consequences (Peters & Büchel, 2011). Every-day choices usually include time and/or risk factors. In line, Weafer, Baggott, and de Wit (2013) categorized laboratory measures of choice impulsivity to quantify either an individual's preference for smaller sooner rewards over larger later rewards (Delay Discounting; DD) or their proclivity for smaller, certain outcomes over larger less certain ones (Probability Discounting; PD).

DD refers to the systematic decrease in the subjective value of a reinforcer as a function of delay to delivery (Rachlin & Green, 1972). Typically, individual parameters of DD are estimated by presenting a series of binary choices between a small but immediate reward and a larger reward available after some time. The subjective value of any amount-delay pair can be estimated and fitted to a discounting function (Mazur, 1987) where the subjective value (V) of an outcome of amount A obtained following delay D declines hyperbolically, and the degree of this devaluation is described by the discounting parameter *k*:

$$[4] \qquad V = \mathrm{A}/(1 + \mathrm{kD})$$

High *k* values reflect steep discounting of delayed outcomes and, therefore, a tendency to favor immediate options, which is considered impulsive. These nonlinear changes in subjective value have been implied to reflect key aspects of the clinical phenomenology among individuals with AUD such as the behavioral manifestation to repeatedly choose the immediate but brief rewards of intoxication despite the knowledge of negative future consequences (Dick et al., 2010). Accordingly, numerous studies have shown higher DD in

individuals with higher levels of alcohol abuse and dependence (see Bickel, Koffarnus, Moody, & Wilson, 2014; MacKillop et al., 2011, p. 2011). Further, steep DD has been associated with earlier onset of AUD symptoms (Dom, D'haene, Hulstijn, & Sabbe, 2006) and has been identified as a predictor for drug relapse following treatment for a range of substances (see Bickel et al., 2014; Sheffer et al., 2014; L. Stevens et al., 2015). Yet, only a few studies have addressed the question whether DD is predictive for relapse to alcohol use following detoxification in AUD patients (de Wilde, Verdejo-García, Sabbe, Hulstijn, & Dom, 2013; Rupp et al., 2016) and no significant associations have been reported so far.

Similar to DD, PD can be assessed through repeated offers of smaller certain and larger probabilistic outcomes systematically varying the reward amount or probability of receiving it (Rachlin, Raineri, & Cross, 1991). Analogous to [4], Equation [5] can be used to evaluate the degree of discounting probabilistic gains or losses,

$$[5] \qquad V = A/(1 + k\theta)$$

with θ being the odds against the event of winning or losing, respectively. Independent from the valence of the outcome, risk aversion is the tendency to choose the certain option while risk seeking behavior means the opposite. Commonly, people have been found to be risk averse facing choices for gains according to the saying "A bird in the hand is worth two in the bush". Such a preference for certain rewards is reflecting steep discounting of probabilistic gains and, thus, high *k* values. In contrast, high *k* values reflecting steep discounting of probabilistic losses represent the tendency to favor probabilistic choices and evidence from empirical data suggests a general bias towards risk seeking when engaging losses (Kahneman & Tversky, 1979).

Diverging from the common choice tendency in the general population by being risk seeking for probabilistic gains is considered as impulsive (Green & Myerson, 2013). However, the interpretation of choice tendencies regarding probabilistic losses in the context of impulsivity is less clear (Green & Myerson, 2013), rendering analyses in cohorts of high impulsive individuals like AUD patients valuable.

In contrast to DD, only few studies have addressed associations of PD with alcohol use and findings have been inconsistent: For probability discounting for gains (PDG), reduced risk aversion was reported for every-day drinkers compared to non- or light drinkers (Ida & Goto, 2009), while other studies showed no association with drinking frequency (Takahashi, Ohmura, Oono, & Radford, 2009) and no differences between alcohol-dependent participants

and matched controls (Myerson, Green, Berk-Clark, & Grucza, 2015). For probability discounting for losses (PDL), the very limited research so far suggests no associations to the frequency of alcohol consumption in a healthy participant sample (Takahashi et al., 2009) and to our knowledge no investigations in patients have been reported, yet.

The above-mentioned gain-loss distinction in the common choice tendencies (risk aversion for gains and risk seeking for losses, i.e. the "reflection effect", Kahnemann & Tversky, 1979) might be understood from an evolutionary perspective: only few positive experiences (e.g. food) offer a significant additional advantage to justify taking a risk to gain even more and thereby risking to get nothing at all, but taking a risk to avoid a single negative experience (e.g. predators) may be essential for survival (McDermott, Fowler, & Smirnov, 2008). Prospect theory, the most successful behavioral model of decision-making under risk, explains these risk attitudes based on the evaluation of losses relative to gains, called "mixed prospects", and introduces the concept of loss aversion (Kahneman & Tversky, 1979). Loss aversion characterizes the tendency to weight the absolute value of losses higher (on average twice as high) as the absolute value of gains when comparing a loss and a gain directly with each other. To evaluate the individual weighting of mixed prospects in experimental settings and estimate the behavioral measure of loss aversion, repeated choices to accept or reject a 50/50% gamble of gaining one amount or losing another amount, have been used in combination with a simple linear model (Tom et al., 2007).

$$[6] \qquad V = 1/2\ (G - \lambda L)$$

The behavioral measure of loss aversion (λ) is computed as the ratio of the contribution of the loss magnitude L and that of the gain magnitude G to the subject's decision. High values of λ reflect a high degree of loss aversion. Although loss aversion has been well described in healthy populations, little research exists in individuals with AUDs. So far, one study reported lower loss aversion in alcohol-dependent patients (Brevers et al., 2014) and a relationship of low loss aversion to high impulsivity has been suggested (Ernst et al., 2014).

It is likely that the cognitive processes involved in choice impulsivity are important during several stages of AUD, including initiation and increase of alcohol use, progression to AUD, seeking and completing treatment, and maintaining abstinence. However, recent studies have emphasized inconsistencies in prior findings, and facets of choice behavior and their association to different stages of AUD remain understudied. This stresses the importance of longitudinal studies to understand how maladaptive patterns of choice behavior develop and

persist, which is critical to identify mechanisms of disease etiology and advancing interventions.

We here report four different facets of impulsive decision making - delay discounting, probability discounting for gains, probability discounting for losses, and loss aversion - in relation to alcohol use and AUD. In Study 3.1, we investigated a sample of social-drinking young male adults, of which some are likely at risk of developing hazardous alcohol use. We examined cross-sectional associations between behavioral choice impulsivity, self-reported personality measures, and patterns of alcohol consumption. Further, we investigated the potential predictive value of baseline choice parameters for trajectories of drinking behavior over a 12-month follow-up interval. In Study 3.2, we assessed differences in choice impulsivity in a group of recently detoxified AUD patients compared to matched control subjects. We analyzed the predictive value of individual decision-making parameters following detoxification for relapse to heavy drinking over a 48-weeks follow-up interval.

4.3 Study 3.1

4.3.1 Material and methods

4.3.1.1 Participants

Participant data was collected within the bicentric longitudinal study on Learning and Alcohol Dependence (LeAD; www.lead-studie.de) conducted in Berlin and Dresden. This study examines mechanisms relevant for the development and maintenance of AUD with a variety of self-report, behavioral, and fMRI measures. Thus, general exclusion criteria were a history of or current neurologic or mental disorders except for nicotine dependence according to DSM-IV-TR (Saß et al., 2003), MRI contraindications (history of severe head trauma, epilepsy, brain or heart surgery, non-removable metal objects or implants in or on participant's body, permanent makeup or tattoos on head or neck, claustrophobia), left-handedness, and no normal or corrected-to-normal vision. The study protocol was approved by the corresponding ethics committees. All subjects gave written informed consent prior to taking part and received a monetary compensation for participation.

Study 1 was conducted with healthy social-drinking young adults, hereafter referred to as Sample 1 (ClinicalTrials.gov identifier: NCT01744834). Participants were randomly sampled from the population of 18-year-old men by the respective local registration office. Women were not included due to their comparatively lower risk of problematic alcohol use (Pabst & Kraus, 2008; Wittchen et al., 2011). Participants were allowed to have a diagnosis of

alcohol abuse according to DSM-IV-TR and had to have had at least two drinking occasions in the past three months. Applying this and general exclusion criteria as mentioned above resulted in a sample of 201 participants from which three had to be excluded after assessment due to screening failure (one subject fulfilled criteria for alcohol dependence, two were abstinent from alcohol in the past three months). Criteria were used to acquire data of social drinkers, of whom some may be at risk for the development of problematic drinking over the course of the following years, some may show stable patterns of alcohol consumption, and some may reduce their alcohol intake without intervention, but none would already have strong behavioral and neural alterations due to prolonged heavy alcohol misuse.

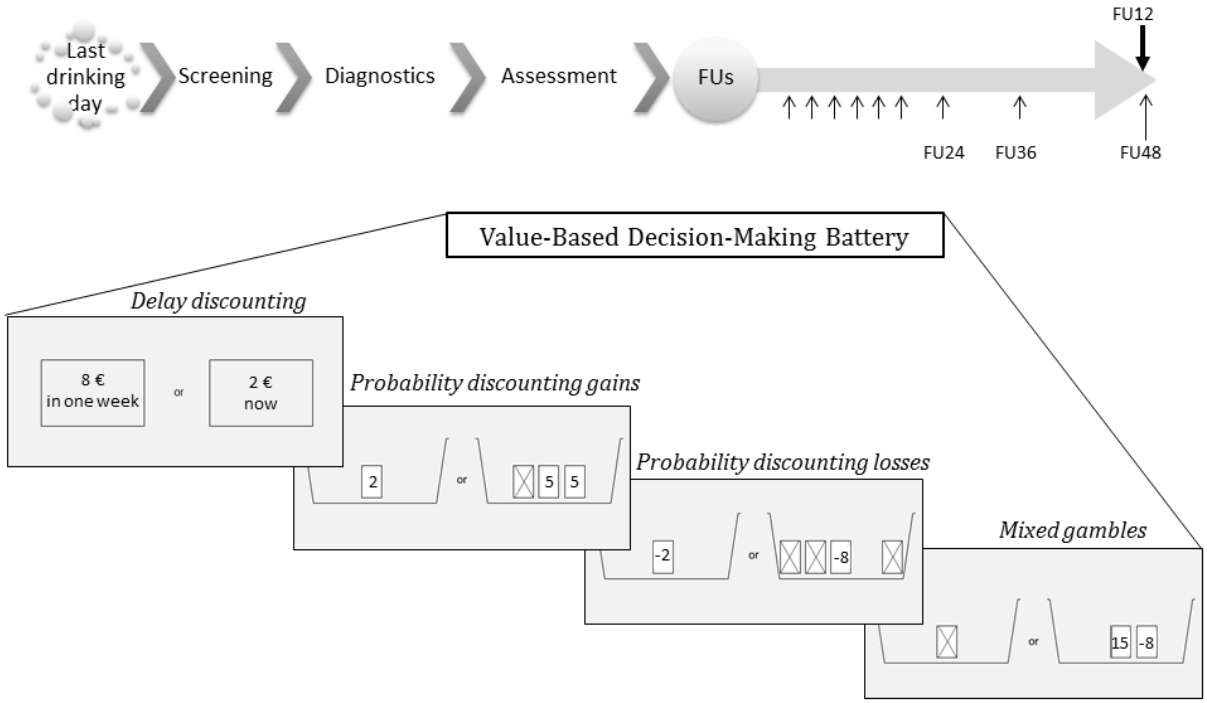

Figure 10. Schematic overview of time course (Study 3.1 and 3.2) and tasks included in the value-based decision-making battery. Upper panel shows the time course of the study procedure. Black arrows indicate time points of follow-ups (FU) to assess drinking trajectories after baseline, where Sample 2 AUD patients (arrows) were regularly contacted and Sample 1 participants (bold arrow) were contacted 12 months after baseline. Below that, the tasks in the computerized value-based decision-making battery to measure different facets of choice impulsivity is shown including delay discounting, probability discounting for gains and losses, and a mixed gambles task.

4.3.1.2 Measures

Procedure

At the baseline assessment, participants were first interviewed using the computer-based German CIDI (Jacobi et al., 2013; Wittchen & Pfister, 1997). This CIDI version includes an extended alcohol section, wherein we collected information about participants' alcohol consumption (Table 5). Baseline drinking data of Sample 1 have previously been used in another publication concerning the association of goal-directed and habitual control with alcohol consumption (Study 1). Next, participants completed several self-report questionnaires about drinking motives, alcohol expectancies, obsessive-compulsive drinking, impulsivity and personality, nicotine dependence, traumatic events, depression and anxiety. These included the BIS-15 (Meule et al., 2011) and the SURPS (Woicik et al., 2009) to assess impulsivity and substance-use related personality traits (i.e. anxiety sensitivity, hopelessness, sensation seeking). At the end of the baseline session, impulsive choice was assessed employing a VBDM battery (Pooseh, Bernhardt, Guevara, Huys, & Smolka, 2017). Twelve months after the baseline assessment, follow-up data (FU12) was collected employing a shortened version of the CIDI via telephone and an online module containing questionnaires (same as baseline).

Value-based decision-making battery

The battery contained four independent tasks: 1) DD to measure the discounting parameter k_D, 2) PDG and 3) PDL to measure the discounting parameter k_O for gains and losses, respectively, and 4) a mixed-gambles task (MG) to measure the degree of loss aversion λ. All tasks were designed in the established format of binary choice presentation. Participants repeatedly had to decide for one of two offers presented simultaneously on a computer screen (Figure 10). Offers were randomly assigned to the left or to the right of the screen. For each trial, the participant's choice was indicated with a red frame before presenting the next offer. There was no time limit for responses and no feedback about the outcomes of choices during the experiment. For each task, subjects were informed that at the end of the experiment one trial was to be selected randomly and credited to their compensation according to their choice. Task parameters were set as follows: for DD, delays were set to the values of 3, 7, 14, 31, 61, 180, and 365 days. Monetary rewards ranged from 0.30 to 10 €. For PDG and PDL, possible probability values were set to 2/3, 1/2, 1/3, 1/4, and 1/5. Amounts ranged from 0.30 to 10 € in PDG and -0.30 to -10 € in PDL. For the MG task, amounts ranged from 1 to 40 € for gains and -5 to -20 € for losses. At the beginning of the task, subjects received 10 € "house money".

Task length for DD, PDG, and PDL was 30, for MG 40 trials. The experiments were presented using Matlab Release 2010a (The MathWorks, Inc., Natick, Massachusetts, United States.) and the Psychtoolbox 3.0.10 based on the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997).

To provide behavioral estimates, a trial-by-trial adaptive Bayesian approach for binary choice presentation was used (Pooseh et al. 2017). The main advantage of this approach is its isochronous adaptive nature. After each trial, the individual choice parameter is estimated and informs the options in the next trial, thus providing the most informative offers near the individual indifference point. This procedure allows for a very efficient inference of behavioral parameters, which are immediately available rendering post hoc parameter inference unnecessary. In addition, the employed implementation supports controlling for unsystematic, illogical data, or simple strategies like always picking the immediate outcome, which could then be considered to be treated as outliers. For a detailed description of the mathematical framework, see Pooseh et al. (2017), and for incorporated differences compared to the task versions used here, see Supporting Information. Differences in the priors of the Bayesian algorithms and the range of monetary outcomes led to generally lower estimates of behavioral parameters in our versions of the tasks. Given that behavioral estimates were assessed with this new approach, the distribution of parameter estimates over task progression was simulated prior to participant data collection to prove the successful implementation of the mathematical framework (Figure S 8-9). Behavioral parameter estimates across all sampled participants converged well and yielded stable final estimates of choice behavior (Figure S 10).

Data analysis

Analyses were done using SPSS (IBM Corp. Released 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Normal distribution of data was tested using Shapiro Wilk tests and visual inspection of Q-Q-plots. Since most variables did not conform to a normal distribution, reported correlations are Spearman's ρ. The corresponding p-values of correlations were computed via Monte Carlo sampling methods with a confidence level of 99% and 10,000 samples. The significance level for all analyses was set to $\alpha \leq .05$ (two-tailed) with False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995) to account for multiple comparisons for each tested hypothesis.

Baseline analyses included correlation of VBDM parameters with alcohol consumption, and measures of personality (BIS-15, SURPS). A composite score ($Drink_{scoreBL}$) was

computed from z-standardized CIDI alcohol consumption items (i.e. estimated alcohol consumption in past year per day, alcohol consumption in past year per drinking occasion, number of binge-drinking events lifetime, and alcohol intake per binge-drinking event). We used a multiple linear regression model to predict the $Drink_{scoreBL}$ with VBDM parameters as independent variables. For longitudinal analyses, we computed difference scores subtracting baseline from follow-up data for all measures of drinking behavior, which were then used to assess the predictive value of VBDM parameters for changes in alcohol consumption over time. Additionally, we built a hierarchical linear regression model adding the BIS-15 subscales as predictors and in a second to fifth step the VBDM parameters separately to examine incremental validity of the VBDM parameters.

4.3.2 Results

4.3.2.1 Sample description

Sample data are presented in Table 5. The group of young adults was rather well educated (Mdn = 12 school years). They reported consumption of alcohol with a median of 1 to 3 drinking occasions per month and 75.3% reported having had at least one binge-drinking event in their life (consumption of at least 60 g alcohol on one occasion). Applying criteria for health risk of alcohol consumption published by the World Health Organization (World Health Organization, 2000) for comparative research purposes, this sample has to be characterized as follows: regarding average alcohol intake per day in the past year, 96.0% have to be characterized as having low-risk (1-40 g), 2.5% as having medium-risk (41-60 g), and 1.5% as having high-risk (61+ g) alcohol consumption; regarding alcohol intake on a single drinking occasion in the past year, 21.7% fall into the low-risk (1-40 g), 30.8% in the medium-risk (41-60 g), 29.8% in the high-risk (61-100 g), and 17.6% in the very-high-risk category (101+ g). In conclusion, most participants had rather few drinking occasions but, when having one, average consumption on that occasion differed greatly between participants. Due to technical issues, behavioral data were missing for four (DD), six (PDG), two (PDL), and seven (MG) participants, respectively. All participants completed the VBDM battery within 20 minutes (M = 16 min 20 sec, SD = 4 min 23 sec), including computerized instructions, offer presentation, algorithmic parameter estimation, and pay-out presentation. Behavioral VBDM estimates are given in Table 5.

Table 5. Descriptive statistics of sociodemographic data, behavioral measures of decision making, questionnaire scores, and measures of alcohol consumption at baseline, 12-month follow up, and their difference in Sample 1.

		Sample 1 (N=198)		
	Gender	♂: 198		
	Smokers (%)	17.20		
		n	*mean*	*SD*
	Age (years) [1]	198	18.38	0.20
VBDM	DD log(k) [1]	194	-4.63	2.22
VBDM	PDG log(k) [1]	192	-0.49	1.04
VBDM	PDL log(k) [1]	196	-0.82	1.63
VBDM	MG log(λ) [1]	191	0.32	0.81
BIS-15	A [1]	195	8.81	1.93
BIS-15	M [1]	196	10.17	2.36
BIS-15	NP [1]	196	11.28	2.79
BIS-15	Sum score	195	30.29	5.20
SURPS	AS [1]	196	10.57	2.26
SURPS	H [1]	196	11.90	2.76
SURPS	IMP [1]	196	9.94	1.98
SURPS	SS [1]	195	16.42	3.11
Baseline	Age of 1st drink [1]	198	14.29	1.37
Baseline	Age of 1st time drunk [1]	190	15.74	1.17
Baseline	Age of 1st binge-drinking event [1]	142	16.50	0.81
Baseline	Est. alcohol consumption in past year (g alc/day) [1]	198	12.01	13.97
Baseline	Alcohol consumption in past year (g alc/drinking occasion) [1]	198	70.45	43.38
Baseline	Number of binge-drinking events lifetime [1]	190	14.91	24.86
Baseline	Alcohol intake per binge-drinking event in past year (g) [1]	198	92.45	67.18
Baseline	$Drink_{scoreBL}$ [1]	198	0.00	3.18
FU12	Est. alcohol consumption in past year (g alc/day) [1]	154	11.10	10.62
FU12	Alcohol consumption in past year (g alc/drinking occasion) [1]	154	61.20	42.43
FU12	Number of binge-drinking events past year [1]	155	10.28	19.59
FU12	Alcohol intake per binge-drinking event in past year (g) [1]	155	109.05	94.99
FU12	$Drink_{scoreFU12}$ [1]	155	-0.07	2.84
Δ FU12-BL	ΔEst. alcohol consumption in past year (g alc/day) [1]	154	-0.86	11.19
Δ FU12-BL	ΔAlcohol consumption in past year (g alc/drinking occasion) [1]	154	-10.39	35.56
Δ FU12-BL	ΔNumber of binge-drinking events past year [1]	148	1.30	18.00
Δ FU12-BL	ΔAlcohol intake per binge-drinking event (g alc) [1]	155	14.06	85.63
Δ FU12-BL	ΔDrinkscore [1]	155	-0.18	2.67

Note: N occasionally differs from 198 for baseline and 155 for FU12 CIDI due to single missing data points. BIS-15 = Barratt Impulsiveness Scale, German short version, with subscales for attentional (A), motor (M), and nonplanning (NP) impulsiveness. SURPS = Substance Use Risk Profile Scale with subscales for AS = anxiety sensitivity; H = hopelessness; IMP = impulsivity; SS = sensation seeking.
[1] Shapiro Wilk Tests and visual inspection of Q-Q-plots implied non-normality of this measure ($p<.05$).

4.3.2.2 VBDM and personality measures

Correlation analysis between behavioral estimates and personality measures showed that steeper DD was associated with higher scores on the BIS-15 non-planning subscale (ρ = .216, p = .003) and the BIS-15 sum score (ρ = .189, p = .008; see Table S 15). In addition, we found a plausible association between lower loss aversion in the MG task with higher

sensation seeking scores (ρ = -.203, p = .004). No further correlation between VBDM parameters and BIS-15 and SURPS survived FDR correction for multiple comparisons. In addition, we explored the intercorrelations between VBDM parameters. We found an association between higher loss aversion and lower risk seeking regarding probabilistic losses (ρ = -.231, p = .001) after FDR correction.

4.3.2.3 VBDM and baseline alcohol consumption

Correlation analysis between behavioral estimates and measures of alcohol consumption showed that steep DD was associated with higher alcohol intake during a binge-drinking event (ρ = .205, p = .004; see Table S 15). No further baseline measure of alcohol consumption was significantly correlated with a VBDM parameter after FDR correction. Prediction of the composite $Drink_{scoreBL}$ with all VBDM parameters showed a small but significant amount of explained variance (see Table 2; smallest value of tolerance in collinearity statistics .933 for MG) with DD constituting the only significant predictor (β = .211, p = .004; all other $|\beta|$s ≤ .112, ps ≥ .130). Beyond that, $Drink_{scoreBL}$ prediction with the three BIS-15 subscales yielded a small but significant proportion of explained variance, and adding the VBDM parameters separately to this second regression model yielded a significant change in explained variance when entering DD (see Table 6; smallest value of tolerance in collinearity statistics .741 for BIS-15 non-planning) showing incremental validity of DD beyond self-reported impulsivity to explain drinking behavior.

4.3.2.4 VBDM and drinking trajectories

At FU12, we collected data about participants' drinking behavior with the CIDI of 78% of Sample 1 (n = 155). With regard to baseline variables, no significant differences were found between participants reached and not reached (all ps ≥ .078). Comparing variables of alcohol consumption at baseline with the respective variable after the 12-month follow-up interval over the whole group, measures of drinking behavior did not change significantly with the exception of lower alcohol consumption per drinking occasion in the past year (exact Wilcoxon Signed Rank tests; Z = -3.55, p < .001; all other ps ≥ .095). But the descriptive within-subject differences of drinking variables for each participant revealed individual changes from baseline alcohol consumption for the majority of the sample: 33% reported greater average consumption per day in the past year (M = +6 g/day in comparison to baseline level, SD = 7 g) and 38% reported lower consumption (M = -7 g, SD = 11 g); regarding average consumption per drinking occasion at FU12 compared to baseline, 24% reported

greater consumption (M = +26 g alc/drinking occasion, SD = 20 g) and 44% reported lower consumption (M = -33 g, SD = 28 g); in regard to binge drinking, 31% reported more binge-drinking events in the past year (M = +13, SD = 20), 33% reported less events (M = -9, SD = 11), and, finally, 35% reported greater consumption per binge-drinking event (M = +72 g/binge-drinking event, SD = 86 g) and 30% reported lower consumption (M = -48 g, SD = 49 g). Changes in drinking behavior yielded no significant associations with any of the VBDM estimates (all *p*s ≥ .082; see Table 6). In line, prediction of the difference in the sum scores of drinking behavior ($\Delta Drink_{score}$) by the baseline decision-making parameters yielded no significant result (see Table 6; smallest value of tolerance in collinearity statistics .910 for MG).

Table 6. Summary statistics of regression analyses predicting baseline drinking behavior and drinking trajectory over 12-month follow up with behavioral VBDM estimates and self-reported impulsivity in Sample 1.

Outcome	Predictors	adj. R^2	*F* change (df)	*p*(*F* change)
$Drink_{scoreBL}$	multiple regression			
	DD log(k), PDG log(k), PDL log(k), MG log(λ)	.039	2.88 (4, 179)	.024
	hierarchical regression			
	BIS-15 A, M, NP	.047	3.95 (3, 177)	.009
	+ DD log(k)	.067	4.86 (1, 176)	.029
	+ PDG log(k)	.066	0.86 (1, 175)	.354
	+ PDL log(k)	.068	1.35 (1, 174)	.247
	+ MG log(λ)	.063	0.04 (1, 173)	.840
$\Delta Drink_{score}$	multiple regression			
	DD log(k), PDG log(k), PDL log(k), MG log(λ)	-.020	0.29 (4, 139)	.884

Note. The effect of adding DD to the hierarchical regression is independent of the order of added predictors. DD = Delay Discounting. BIS-15 = Barratt Impulsiveness Scale, German short version, with subscales for attentional (A), motor (M) and non-planning (NP) impulsiveness . MG = Mixed Gambles. PDG = Probability Discounting for Gains. PDL = Probability Discounting for Losses.

4.4 Study 3.2

4.4.1 Material and methods

4.4.1.1 Participants

Study 3.2 was conducted with treatment-seeking alcohol-dependent patients and matched control participants hereafter referred to as Sample 2 (ClinicalTrials.gov identifier: NCT01679145). General exclusion criteria were the same as in Study 1. This sample consisted of 114 alcohol-dependent patients (16% female) and 98 matched control participants (17% female). Control participants were sought via advertisements in the area of the Universitätsklinikum Dresden and Campus Charité Mitte and in newspapers. Interested

persons were screened for the inclusion and exclusion criteria and matched with the patient group for age, gender, smoking status, and educational background. Patients had a diagnosis of alcohol dependence for a minimum of three years and had gone through detoxification procedures on average four times (SD 4.5; range 1-20). At time of testing, patients were abstinent from alcohol on average 17 days (SD = 10 d; range 4-50 d), showed no signs of alcohol withdrawal (CIWA (Stuppaeck et al., 1994), score ≤ 3), and had a result of zero in a breath-alcohol test. Patients were followed up for 48 weeks. They were contacted (alternating phone and personal appointments) every 2 weeks for 3 months, then again 24, 36 and 48 weeks after baseline assessment (Figure 10). We assessed relapse to heavy drinking defined as consumption of ≥ 60/48 (male/female) gram of alcohol in one drinking occasion and the amount of alcohol consumption using the Timeline Follow-Back (Sobell & Sobell, 1992). In addition, we verified the relapse status of patients with their PEth levels at the follow-up assessments after 12 and 24 weeks. A value of 112ng/ml or higher was set as cut-off marker for heavy drinking (Schröck, Wurst, Thon, & Weinmann, under review). Phosphatidylethanol levels were only acquired for 58 and 64 patients at follow up after 12 and 24 weeks, respectively, due to temporary drop out for these time points (n = 41 and n = 37, respectively) and organizational constraints. Twelve patients were classified as relapsers despite their self-reported abstinence due to increased PEth blood levels at least at one of the follow-up assessments. Three of those twelve patients were drop outs at the last follow-up assessment. At the end of the follow-up interval after 48 weeks, we had reached 75% (n = 85) of the patients. Furthermore, there were two patients classified as abstainers who consumed alcohol during the follow-up interval (two and six standard drinks, respectively, over 48 weeks) but never reached the critical threshold for relapse of at least five drinks on one occasion.

4.4.1.2 Measures

The procedure of assessment, CIDI, and the VBDM tasks were the same as in Study 1. In addition, the severity of alcohol dependence was assessed using the ADS (Horn et al., 1984). Current alcohol craving was assessed with the OCDS-G (Mann & Ackermann, 2002). Additionally, symptoms of Anxiety and Depression were assessed with the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983).

4.4.1.3 Data analysis

Survival analyses were done with the survival package (version 2.38-3; Therneau, 2015; Therneau & Grambsch, 2000) implemented in R (version 3.2.2; R Development Core Team,

2008). Group comparisons between patients and controls were performed using non-parametric Mann-Whitney U-tests. Analysis of relapse prediction over 48 weeks was done with two analytical strategies: first, with a Cox proportional-hazard regression model using VBDM parameters as covariates to investigate the continuous relationship between hazard for relapse and behavioral decision making, and second, with exact Mann-Whitney U-tests comparing prospective relapsers and abstainers. Additionally, we tested the associations of alcohol dependence severity (ADS), obsessive-compulsive drinking and craving (OCDS-G), anxiety (HADS-A) and depression scores (HADS-D) on time to relapse using Cox regression with the VBDM parameters and those four covariates included. VBDM parameters and covariates were z-standardized before being entered in the Cox regression model for better interpretability and comparability of the hazard ratios.

4.4.2 Results

4.4.2.1 Sample description

Sample data are presented in Table 7. Groups did not differ in gender distribution, mean age, and proportion of current smokers but in SES. Due to technical issues, data for DD, PDG, and MG was missing for three and for PDL for two control participants. Participants completed the VBDM battery on average within 20 minutes (M = 18 min 32 sec, SD = 4 min 21 sec). There were neither statistical differences between groups in the time needed for battery completion ($t(184) = 1.74$, $p = .083$) nor in the median deliberation time before making a decision in any of the four tasks (DD: controls M = 3.6±1 s, patients M = 3.7±1.3 s, $t(202) = -.641$, $p = .409$; PDG: controls M = 2.5±0.9 s, patients M = 2.5±1 s, $t(204) = .055$, $p = .956$; PDL: controls M = 2.5±1.1 s, patients M = 2.3±1.2 s, $t(202) = .917$, $p = .360$; MG: controls M = 1.8±0.7 s, patients M = 1.7±0.7 s, $t(206) = -.399$, $p = .690$).

4.4.2.2 VBDM in patients vs. control participants at baseline

Correlations between VBDM measures, personality measures, and alcohol consumption for patients and control participants can be found in Table S 16. Group comparisons between patients and controls showed significant differences in all four behavioral measures of VBDM: higher delay discounting (Cohen's $d = 0.45$), lower risk aversion regarding gains ($d = 0.46$), lower risk seeking regarding losses ($d = 0.44$), and lower loss aversion ($d = 0.61$) in patients compared to control participants (Figure 11, Table 7). These group differences were still significant when controlling for SES (all adj. R^2s > .022, all Fs > 5.088, all ps < .025) and

smoking status (all adj. R^2s > .029, all Fs > 6.209, all ps < .013) in separate univariate ANOVAs.

Table 7. Descriptive statistics of sociodemographic data, behavioral measures of choice impulsivity, questionnaire scores, and measures of alcohol consumption in Sample 2.

		Sample 2 (N=212)							
		Alcohol-dependent patients (n=114)			Healthy controls (n=98)			Statistical difference test value	*p*
Sex		♀: 18; ♂: 96			♀: 17; ♂: 81			0.09 [a]	.853 [e]
Smokers (%)		76.3			65.3			3.12 [a]	.094 [e]
		n	*mean*	*SD*	n	*mean*	*SD*		
Age (years) [1]		114	44.77	10.56	98	43.75	10.86	-0.87 [b]	.388 [e]
SES[1]		113	-0.15	0.67	93	0.20	0.64	-3.67 [b]	**<.001** [e]
HADS-A [1]		114	4.42	3.43	97	2.34	2.10	-4.74 [b]	**<.001** [e]
HADS-D [1]		114	3.79	3.68	97	1.79	2.25	-4.48 [b]	**<.001** [e]
VBDM	DD log(k) [1]	114	-3.17	3.53	95	-4.40	2.98	-3.15 [b]	**.002** [e]
VBDM	PDG log(k) [1]	114	-1.14	2.52	95	-0.30	1.87	-3.21 [b]	**.001** [e]
VBDM	PDL log(k) [1]	114	-1.73	2.79	96	-0.67	2.62	-3.09 [b]	**.002** [e]
VBDM	MG log(λ) [1]	114	-0.43	1.24	95	0.13	1.25	-4.21 [b]	**<.001** [e]
BIS-15	A [1]	108	9.23	2.62	96	8.56	2.16	-1.80 [b]	.071 e
BIS-15	M [1]	109	10.30	2.58	97	9.66	2.32	-1.90 [b]	.058 [e]
BIS-15	NP [1]	108	11.93	3.32	97	10.97	3.17	-1.94 [b]	.053 [e]
BIS-15	Sum	107	31.53	6.62	96	29.14	5.67	-2.76 [c]	**.006**
Est. alcohol consumption in past year (g alc/day) [1]		114	177.78	137.68	98	11.23	13.07	-11.68 [b]	**<.001** [e]
Alcohol consumption in past year (g alc/drinking occasion) [1]		114	206.92	125.94	98	42.80	31.92	-11.68 [b]	**<.001** [e]
Number of binge-drinking events lifetime [1]		104	496.63	428.08	95	70.71	161.14	-8.16 [b]	**<.001** [e]
Alcohol intake per binge-drinking event in past year (g alc) [1]		114	276.95	157.37	98	93.21	92.61	-10.21 [b]	**<.001** [e]
Cumulated lifetime alcohol intake (kg alc) [1d]		114	1749.1	1096.0	98	284.45	810.35	-11.36 [b]	**<.001** [e]
DSM-IV Abuse symptoms [1]		114	1.46	1.19	98	0.09	0.32	-	-
DSM-IV Dependence symptoms [1]		108	5.65	1.27	98	0.43	0.90	-	-
DSM-V AUD symptoms [1]		108	7.58	2.18	98	0.53	1.07	-	-
ADS sum score [1]		113	14.69	6.74	98	1.86	2.83	-11.88 [b]	**<.001** [e]
OCDS-G total score [1]		109	11.81	8.36	97	2.64	2.84	-9.28 [b]	**<.001** [e]

Note: N occasionally differs from 212 due to single missing data points. Bold printed values survive Benjamini-Hochberg FDR correction. Socioeconomic status (SES) was computed as the sum of z-transformed social status, household income and inverse personal debt scores (Garbusow et al., 2015; Schmidt, Gastpar, Falkai, & Gäbel, 2006). ADS = Alcohol Dependence Scale. BIS-15 = Barratt Impulsiveness Scale, German short version, with subscales for attentional (A), motor (M) and nonplanning (NP) impulsiveness. DD = Delay Discounting. HADS = Hospital Anxiety and Depression Scale with subscales for anxiety (A) and depression (D). MG = Mixed Gambles. OCDS-G = Obsessive Compulsive Drinking Scale, German version. PDG = Probability Discounting for Gains. PDL = Probability Discounting for Losses.

[1] Shapiro-Wilk test implied non-normal distribution of this measure (p<.05).

[a] Pearson χ2 (Exact χ2 test)

[b] Z (Exact Mann-Whitney U-test)

[c] t (t-test)

[d] Prior to detoxification in alcohol-dependent patients

[e] exact p-value calculated with permutation test

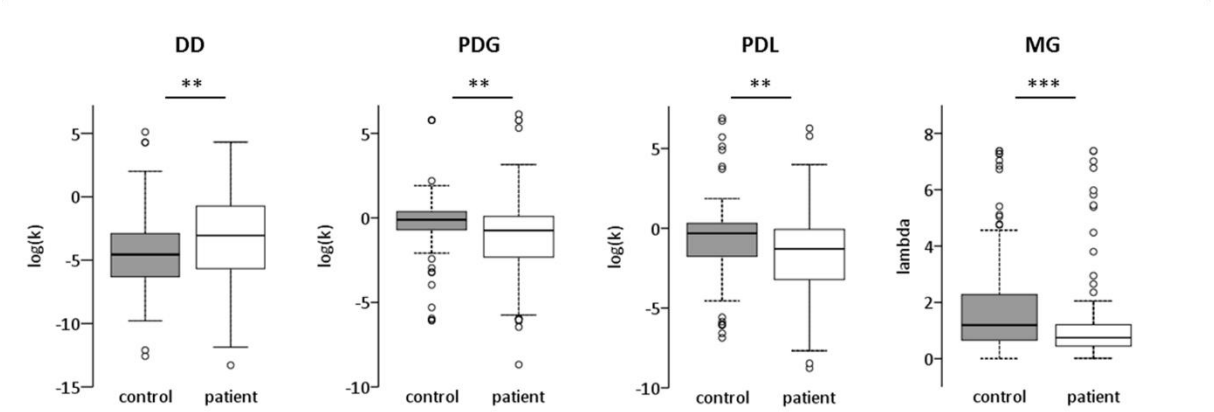

*Figure 11. Group comparisons for behavioral estimates of choice impulsivity between AUD patients and control participants (Study 3.2). All four facets are found to differ significantly between the groups. AUD patients (white) showed higher discounting rates in DD, lower discounting rates in PDG and PDL, and lower loss aversion than control participants (grey). DD = delay discounting, PDG = probability discounting for gains, PDL = probability discounting for losses, MG = Mixed Gambles task. ** p < .01, *** p <.001*

4.4.2.3 VBDM and relapse prediction

Of the 85 AUD patients we had reached for the final follow-up assessment after 48 weeks, 32% (n = 27) remained abstinent while 68% (n = 58) relapsed (see Table 8 for descriptive statistics and group comparisons and Figure 12 for the Kaplan-Meier survival plot) [3]. Patients we reached did not differ significantly from those we did not reach regarding the variables reported in Table 8 (Mann-Whitney U-tests, all Zs $\leq |1.70|$, all ps $\geq .091$). We tested whether VBDM parameters were associated with the risk to relapse with Cox proportional-hazard regression models with the complete sample of patients (N = 114; n = 45 abstainers, n = 69 relapsers). The Cox regression model was overall significant (see Table 9) and fulfilled the assumption of proportional hazards ($\chi^2(4) = 4.41$, $p = .353$). The covariates DD and PDL were significant predictors of relapse in this regression model (but note that the regression coefficients of DD increased over time, did not fulfill the assumption of proportional hazards over the observation period, and, thus, must be interpreted with caution; Spearman's $\rho = .23$, $p = .041$). The other two VBDM parameters were not significantly associated with relapse (see Table 9). Exact Mann-Whitney U-tests comparing abstainers and relapsers corroborated the finding regarding PDL by showing significantly lower risk seeking for losses in prospective relapsers (see Table 8) in the subgroup of patients completing the follow-up interval, while there were no significant differences in the other VBDM parameters (see Table

[3] Numbers of abstaining and relapsing patients differ from Study 2 due to different sample sizes completing the behavioral paradigms (Two-Step in Study 2 and VBDM battery in Study 3), and the inclusion of PEth information to classify relapsers here and information from relatives to classify relapsers in Study 2.

8). Interestingly, a post hoc exact Mann-Whitney U-test revealed no significant difference between controls and abstainers for PDL (Z = -0.70, p = .490).

Table 8. Descriptive statistics of sociodemographic data, behavioral measures of choice impulsivity, questionnaire scores, and measures of alcohol consumption in the patients of Sample 2 compared between abstainers and relapsers during the 48-week follow-up interval.

		Abstaining patients (n=27)			Relapsing patients (n=58)			Statistical difference	
								test value	*p*
Sex		♀: 7; ♂: 20			♀: 7; ♂: 51			2.57 [a]	.126 [d]
Smokers (%)		74.1			75.5			0.03 [a]	>.999 [d]
		n	*M*	*SD*	n	*mean*	*SD*		
Age (years)		27	44.14	13.06	58	46.03	10.22	-0.82 [b]	.415 [d]
SES		27	-0.17	0.60	57	-0.14	0.66	-0.59 [b]	.559 [d]
HADS-A		27	4.22	2.74	58	4.57	3.58	-0.11 [b]	.915 [d]
HADS-D		27	3.56	2.94	58	4.09	4.03	-0.05 [b]	.964 [d]
VBDM	DD log(k)	27	-2.85	3.01	58	-3.49	3.61	-0.62 [b]	.539 [d]
	PDG log(k)	27	-0.88	2.06	58	-1.33	2.85	-1.76 [b]	.080 [d]
	PDL log(k)	27	-0.89	1.94	58	-2.27	2.92	**-2.30 [b]**	**.021 [d]**
	MG log(λ)	27	-0.24	0.96	58	-0.34	1.35	-0.63 [b]	.532 [d]
BIS-15	A	26	8.81	2.55	56	9.50	2.43	-1.04 [b]	.301 [d]
	M	27	9.70	2.38	56	10.71	2.59	-1.55 [b]	.122 [d]
	NP	27	11.41	3.57	55	12.18	3.08	-1.03 [b]	.308 [d]
	Sum	26	30.19	6.85	55	32.40	6.00	-1.18 [b]	.242 [d]
Est. alcohol consumption in past year (g alc/day)		27	160.11	97.45	58	174.87	122.50	-0.29 [b]	.772 [d]
Alcohol consumption in past year (g alc/drinking occasion)		27	190.33	96.28	58	206.53	105.50	-0.63 [b]	.532 [d]
Number of binge-drinking events lifetime		26	567.65	437.51	53	446.77	438.81	-1.04 [b]	.301 [d]
Alcohol intake per binge-drinking event in past year (g alc)		27	258.67	112.23	58	290.02	155.17	-0.66 [b]	.516 [d]
Cumulated lifetime alcohol intake (kg alc) [c]		27	1677.32	1207.02	58	1893.29	1139.54	-0.88 [b]	.385 [d]
DSM-IV Abuse symptoms		27	1.22	1.05	58	1.69	1.22	-1.76 [b]	.080 [d]
DSM-IV Dependence symptoms		25	5.84	1.25	57	5.79	1.18	-0.27 [b]	.784 [d]
DSM-V AUD symptoms		25	7.72	1.97	57	7.93	2.12	-0.47 [b]	.640 [d]
ADS sum score		27	14.67	7.06	57	15.00	6.14	-0.35 [b]	.733 [d]
OCDS-G total score		26	11.27	8.04	56	10.95	7.61	-0.01 [b]	.998 [d]

Note: N occasionally differs from 27 and 58, respectively, due to single missing data points. Bold printed statistics survive Benjamini-Hochberg FDR correction. Socioeconomic status (SES) was computed as the sum of z-transformed social status, household income and inverse personal debt scores (Garbusow et al., 2015). ADS = Alcohol Dependence Scale. BIS-15 = Barratt Impulsiveness Scale, German short version, with subscales for attentional (A), motor (M) and nonplanning (NP) impulsiveness. DD = Delay Discounting. HADS = Hospital Anxiety and Depression Scale with subscales for anxiety (A) and depression (D). MG = Mixed Gambles. OCDS-G = Obsessive Compulsive Drinking Scale, German version. PDG = Probability Discounting for Gains. PDL = Probability Discounting for Losses.

[a] Pearson χ^2 (Exact χ^2 test)

[b] Z (Exact Mann-Whitney U-test)

[c] Prior to detoxification

[d] exact p-value calculated with permutation test

Table 9. Summary statistics of Cox proportional hazards regression analyses predicting time to relapse with behavioral VBDM estimates, AUD severity, and scores of anxiety and depression in the patients of Sample 2.

Model	Predictors	R^2	χ^2 (df)	p	HR	95% CI	p
Model 1		**.11**	**12.65 (4)**	**.013**			
	DD log(k)				0.75	0.58-0.97	.029
	PDG log(k)				0.87	0.68-1.12	.282
	PDL log(k)				0.71	0.56-0.92	.008
	MG log(λ)				0.92	0.71-1.18	.491
Model 2	ADS	<.01	0.41 (1)	.521 †	1.08	0.85-1.37	.518
Model 3	OCDS-G	<.01	0.07 (1)	.792 †	1.03	0.82-1.31	.791
Model 4	HADS-A	.03	3.95 (1)	.047 †	1.28	1.01-1.63	.041
Model 5	HADS-D	.02	2.10 (1)	.147	1.20	0.95-1.51	.136
Model 6		.14	16.68 (8)	.034			
	DD log(k)				0.76	0.58-1.00	.053
	PDG log(k)				0.95	0.73-1.23	.686
	PDL log(k)				0.67	0.51-0.88	.004
	MG log(λ)				0.98	0.75-1.28	.902
	ADS				1.11	0.80-1.55	.524
	OCDS-G				0.86	0.64-1.16	.321
	HADS-A				1.16	0.86-1.58	.331
	HADS-D				1.15	0.85-1.55	.360

Note. Bold printed statistics survive Benjamini-Hochberg FDR correction. ADS = Alcohol Dependence Scale (Skinner & Horn, 1984). DD = Delay Discounting. HADS = Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) with subscales for anxiety (A) and depression (D). MG = Mixed Gambles. OCDS-G = Obsessive Compulsive Drinking Scale, German version (Mann & Ackermann, 2000). PDG = Probability Discounting for Gains. PDL = Probability Discounting for Losses.

† Assumption of proportional hazards not met by this regression model ($p<.05$).

In addition, we examined the association of alcohol dependence severity (ADS), obsessive-compulsive drinking and craving (OCDS-G), anxiety (HADS-A) and depression (HADS-D) with relapse rates and the stability of the aforementioned findings when integrating these clinically relevant variables as covariates in the relapse analysis. Therefore, we did additional Cox regression analyses: first, separate analyses for those four covariates to check for their association with relapse rates on their own, and second, adding these four covariates to the model with the VBDM parameters. First, although anxiety levels had a significant effect on relapse rates on their own (see Table 9), this model did not meet the assumption of proportional hazards over the whole follow-up period (regression coefficients decreasing over time; Spearman's ρ = -.32, p = .016) and, thus, should not be interpreted. The other models did not yield significant effects (see Table 9). Second, the Cox regression model with all eight predictors was overall significant (see Table 9) and fulfilled the assumption of proportional hazards ($\chi^2(8)$ = 13.12, p = .108). The covariate PDL was still a significant predictor of relapse, while DD was not anymore. Predictability of relapse by PDG and MG did not change.

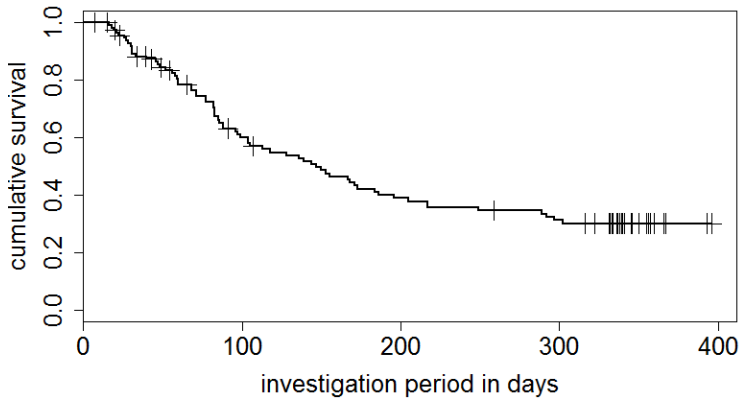

Figure 12. Survival plot displaying treatment outcome in AUD patients (Study 3.2). From the last reported drinking occasion to the end of the follow-up period on average 48 weeks later, 32% of patients included in the study did not relapse to heavy drinking. Vertical lines indicating censored data (drop out or end of follow-up interval, respectively).

4.5 Discussion

We evaluated different behavioral measures of impulsive decision making in 1) social-drinking young adults and 2) alcohol-dependent patients compared to control participants within a cross-sectional and longitudinal design. In Study 3.1, we found steeper delay discounting at baseline to be associated with more severe binge-drinking events in young adults, but neither delay nor probability discounting or loss aversion could predict changes of alcohol consumption in the one-year follow-up. In Study 3.2, we confirmed significantly higher rates of delay discounting in early abstinent AUD patients compared to controls. Moreover, patients showed lower rates of probability discounting for gains and losses as well as lower loss aversion. Finally, low rates of probability discounting for losses were found to predict relapse to heavy drinking within one year.

DD rates in the young adult social-drinkers did explain baseline drinking behavior above and beyond aspects of self-reported impulsivity, indicating an association of DD with alcohol consumption that is at least partially independent from other facets of impulsivity. The strongest association of DD was found with the amount of alcohol consumed per binge-drinking event, which is in line with the assumption that it is associated with alcohol abuse rather than simply alcohol use (MacKillop et al., 2011). In this non-clinical sample, neither PD, in line with a previous report (Takahashi et al., 2009), nor loss aversion was associated with alcohol consumption. Interestingly, associations between heavy, frequent binge-drinking and disadvantageous performance were found in the Iowa Gambling Task (IGT) in young adults (Goudriaan, Grekin, & Sher, 2007). The IGT measures risk preferences and disadvantageous choices for immediate gains resulting in overall losses in the long run. Thus,

associations between drinking and the IGT might also be related to "myopia of choice" behavior reminiscent of delay discounting procedures and, therefore, in line with our results.

DD rates at baseline did not predict future alcohol consumption in our young-adults sample. Contrary to this finding, Audrain-McGovern et al. (2009) reported an association between DD in 15-year-old participants and smoking trajectories over the following four years. Besides the fact that we investigated alcohol instead of tobacco consumption, this discrepancy could also be attributed to the different age of our subjects or the shorter observation time. For example, a recent study could predict alcohol consumption trajectories employing self-report measures over a four-year follow up but not for shorter timespans (Jurk, Mennigen, Goschke, & Smolka, 2016). An alternative explanation is the relative small observed difference in the pattern of alcohol consumption. Although individual changes in drinking behavior were substantial in some participants, others did not report any changes and, furthermore, reported changes were rather small in absolute values. However, our findings are in line with animal models of DD, illustrating predictive power for later drug self-administration for nicotine but not for alcohol (Diergaarde, van Mourik, Pattij, Schoffelmeer, & De Vries, 2012). Likewise, none of the behavioral measures of decision making under risk showed a predictive value for future drinking trajectories, which had not been addressed before but might corroborate the suggestion that not initial levels of risk taking but its increment over time may contribute to subsequent alcohol use in adolescence (MacPherson, Magidson, Reynolds, Kahler, & Lejuez, 2010).

As anticipated, AUD patients were found to be more impulsive than control participants according to self-report (BIS) and steeper discounting of delayed monetary rewards. Additionally, AUD patients exhibited shallower discounting of probabilistic gains and losses compared to controls. Within the theoretical conceptualization of risk attitudes, a general bias towards risk taking in AUD patients is in line with reduced risk aversion for probabilistic gains, but cannot explain our observation of reduced risk seeking for losses. In contrast, a general bias to overestimate the likelihood of probabilistic outcomes could explain choice behavior for both probabilistic losses and gains. Such a bias would lead to overestimating the likelihood of a probabilistic gain and thus result in higher risk taking in PDG, which is generally considered a facet of impulsive choice behavior (Green & Myerson, 2013). The same bias, i.e. overestimating the likelihood of a probabilistic loss, would lead to less risk seeking in the PDL task and, thus, seemingly less impulsive choices from a risk-taking perspective. Given the increased impulsivity of patients in all other self-report and behavioral measures, we rather interpret the lower risk seeking regarding probabilistic losses that was

also associated with poorer treatment outcome, as impulsive choice tendency. Replication of our findings and further elaboration on this combination of risk and loss attitudes is clearly needed in a clinical context.

Within non-clinical samples, measures of PDG and PDL were shown to be negatively correlated (Shead & Hodgins, 2009), though not always significantly so (Mitchell & Wilson, 2010). This was interpreted as a general risk attitude independent from the valence of the outcome, that is, people being relatively more risk seeking for gains were assumed to also be relatively more risk seeking for losses. Considering the significantly lower discounting parameters for both PDG and PDL in patients compared to controls and the positive correlation between PDG and PDL in patients in relation to the negative correlation in control participants, we might suppose that behavioral preferences regarding gains and losses develop in different directions in the course of the manifestation of AUD. Though this is highly speculative, given that a gain-loss asymmetry is well-established (e.g. Estle, Green, Myerson, & Holt, 2006) and that differential neurobiological manifestations in distinct brain regions are activated in response to monetary gains and losses (Liu, Hairston, Schrier, & Fan, 2011), a divergent development is not implausible. Overall, our findings thus imply differences in impulsive choice within the gain and loss domain in patients and suggest alterations in the differential evaluation of gains and losses in AUD rather than in general risk attitudes.

In line with previous findings for cocaine and alcohol users (Brevers et al., 2014; Meade, Young, Mullette-Gillman, Huettel, & Towe, 2014), AUD patients in our study exhibited significantly lower rates of loss aversion than controls. Again, this might represent higher levels of impulsivity and could be interpreted within the concept of reduced punishment sensitivity. Reduced punishment sensitivity in behavioral performance in SUDs has been shown repeatedly and a diminished neural response to monetary losses in the striatum and anterior cingulate cortices has been shown in neuroimaging studies (Bechara, Dolan, & Hindes, 2002; Beck et al., 2009; Bjork, Momenan, Smith, & Hommer, 2008; Wrase et al., 2007). Taken together, our findings regarding probability discounting and loss aversion could be explained by a general tendency to overestimate the probability of uncertain outcomes (both gains and losses in the probability discounting paradigms) as well as reduced punishment sensitivity (reduced loss aversion).

Due to their importance as candidate behavioral markers for addiction, we further tested whether DD rates were predictive for relapse in the treatment of alcohol-dependent patients. A set of studies demonstrated such a relation for different drug-dependent populations such as nicotine and cocaine in the way that more impulsive patients showing steeper DD were more

likely to relapse (Bickel et al., 2014). Group comparisons between abstainers and relapsers in our study did not support such a relationship, while Cox regression analysis showed an association in the opposite direction of steeper DD being related to a decreased hazard for relapse. Additionally, the Cox regression model suggests a time-varying relationship between DD and abstinence in detoxified AUD patients, which hampers the interpretation of this finding. Taking these results, prior findings (de Wilde et al., 2013; Rupp et al., 2016) and the possibility of unpublished studies not demonstrating a relationship between DD and abstinence from alcohol (Bickel et al., 2014), rates of DD might not represent a reliable predictor for treatment success in AUD.

To our knowledge, we were the first to investigate how behavioral measures of PDG, PDL, and loss aversion correlate with relapse to heavy drinking. We provide evidence for choice behavior involving probabilistic losses to discriminate patients relapsing to heavy drinking from abstinent patients, which show *k* values comparable to the control group (i.e. more risk seeking). Besides this categorical prediction, shallower discounting also predicted a greater hazard for relapse in our sample. Perhaps behavior in this choice paradigm was sensitive to predict relapse because it combines subjects' attitudes towards risk (i.e. overestimating the likelihood of the uncertain loss) and towards losses (i.e. reduced punishment sensitivity), and showing alterations in both constructs makes patients more vulnerable for prospective relapse. This interpretation would also be in line with Green and Myerson's (2013) hypothesis of multiple impulsivities, which could in combination increase the risk for certain pathologies.

Present findings should be interpreted in the light of several limitations. We used a rather new mathematical approach to obtain behavioral estimates. That is why we examined properties of the paradigms themselves beyond the investigation of the relation between behavioral measures of VBDM and alcohol consumption. In line with previous results and indicating validity, we found that DD was selectively associated with self-reported trait impulsivity (convergent validity) but not with anxiety sensitivity, hopelessness, and sensation seeking (divergent validity; H. de Wit, Flory, Acheson, McCloskey, & Manuck, 2007; Koff & Lucas, 2011; Mobini, Grant, Kass, & Yeomans, 2007). Further, we employed a limited range and rather small values of monetary outcomes in all four tasks. Though clearly sufficient to illustrate group differences for AUD and control subjects on a cross-sectional level, longitudinal predictions might have been strengthened through enhanced conflict between choices involving winning or losing larger amounts of money. Next, AUD patients in this study were treatment-seeking, and therefore results may not reflect outcomes for the large

group of alcohol-dependent persons not seeking treatment. Likewise, our young adult sample did not include women hence impeding generalization of our findings. We might argue that this sample is more likely to include individuals at risk of the development of future AUD symptoms since women show decreased rates of alcohol abuse and dependence and differences in impulsivity (Nederkoorn, Baltus, Guerrieri, & Wiers, 2009). However, due to the small changes in alcohol consumption within the limited observation time in our longitudinal design, results must be interpreted carefully and extended observation of the development of drinking trajectories should be awaited.

In conclusion, our findings suggest systematic alterations in different facets of impulsive choice behavior after chronic, heavy alcohol use. While supporting the notion of delay discounting as behavioral marker for AUD, confidence in its ability to prospectively predict alcohol consumption or treatment outcome remains weak. Meanwhile, impulsive choice behavior involving risks might undergo a developmental change that parallels alcohol consumption indicated by the robust alterations in alcohol-dependent patients and the suggested association to treatment outcome. Combining our results of both samples thereby indicates that the parameters of impulsive choice are less relevant as risk factors predisposing for alcohol consumption in healthy young adults and its trajectory over one year, but instead might rather be a consequence of prolonged risky drinking. Of course, our data does not conclusively rule out the possibility that there might be a subgroup of young-adult social drinkers, in which decision making could predict later onset of AUD symptoms. The ongoing longitudinal assessment of these subjects might shed light on this issue. Nevertheless, our findings may bear important clinical implications. They underline the importance of using neurocognitive measures when identifying high relapse risk patients in clinical populations and, more generally, stress the relevance of promoting treatment interventions targeting decision-making abilities.

Chapter 5. General discussion

5.1 Summary of findings and discussion

The three presented studies investigated the association between VBDM and alcohol use (disorder). In Study 1, we showed that model-free and model-based RL as operationalization of habitual and goal-directed behavioral control, respectively, were not related to alcohol consumption in young adult social drinkers on a behavioral and neural level, except for an exploratory finding of stronger BOLD responses to the model-free RPE in putamen in early-onset drinkers. In Study 2, we could not replicate our previous findings of the pilot study (Sebold et al., 2014) in a larger sample, that is, we did not find a difference in model-based strategies between AUD patients and control participants. However, we found that model-based control interacted with alcohol expectancies. Subsequently relapsing AUD patients showed high model-based control but low alcohol expectancies or vice versa, while model-based control and alcohol expectancy were positively correlated in abstaining patients. Furthermore, relapsing AUD patients showed decreased BOLD responses to the model-based signal in vmPFC compared to control participants and abstaining patients. In Study 3, we showed systematic differences in VBDM regarding delays, risks, and valence of monetary outcomes between AUD patients and control subjects, that is, AUD patients showed stronger delay discounting, were less risk averse in the gain domain, less risk seeking facing losses, and less loss averse. Moreover, individual levels of a risk-seeking tendency when facing losses were found to be predictive of relapse within one year. However, we did not find an association with alcohol consumption in general in young adult social drinkers on a cross-sectional level and no predictive value for the change of alcohol consumption one year later.

In summary, there was no indication of a general imbalance between goal-directed and habitual control in association with non-pathological alcohol consumption and AUD. This contrasts with the assumptions of current etiological models of AUD (Everitt & Robbins, 2016; Redish et al., 2008) and adds to the mixed findings of previous studies (Gillan et al., 2016; Reiter et al., 2016; Sebold et al., 2014; Sjoerds et al., 2013; Voon et al., 2014). In addition, choice biases regarding modulating features of option valuation – delay, risk, and valence – seem not to be predisposing factors for non-pathological alcohol consumption in young adults. On the contrary, all examined modulators were systematically altered in AUD, which is in line with previous reports for delays (MacKillop et al, 2011) and extends the literature considerably for the other three modulating features. These findings have sizable consequences for our current understanding of AUD and its etiology.

5.1.1 Goal-directed and habitual decision making and alcohol use (disorder)

There was no indication that goal-directed and habitual decision making would be a predisposing risk factor for non-pathological alcohol use per se. Additional analyses yielded no significant association between measures of model-free and model-based control in the Two-Step task and drinking behavior twelve months after baseline assessment (see Appendix D). Furthermore, there were no general differences in these processes between AUD patients and control participants or abstaining and relapsing AUD patients. These findings do not support the assumption of a generalized shift from goal-directed to habitual decision making in AUD. This is puzzling given the widespread belief that SUDs must be at least partially a result of an emerging dominance of habitual behavioral control (e.g. Everitt & Robbins, 2016; Redish et al., 2008; Vandaele & Janak, 2017; Voon et al., 2017). Assuming our results would be replicated, this would speak against this common view. Consequently, the dual-system accounts proposing a shift from goal-directed to habitual behavioral control could be either abandoned, modified, or extended.

Abandoning the dual-system accounts of SUD completely would be premature. There is some evidence for the control shift in the domain of cocaine and methamphetamine use disorders (Ersche et al., 2016; Voon et al., 2014) and most SUDs have often been assumed to comprise similar psychological and neurobiological mechanisms (Volkow & Baler, 2014) due to their common effects on dopaminergic signaling in the VTA and its innervated regions in striatum and PFC (Volkow et al., 2013). Furthermore, many investigations in rodent models of addiction have yielded supportive findings for the shift from goal-directed to habitual control when using drugs of abuse as outcomes (e.g. Clemens et al., 2014; Corbit et al., 2012; Dickinson et al., 2002; Miles et al., 2003; Nordquist et al., 2007). However, as the translation of these findings to the domain of human AUD was rather unsuccessful so far, the validity of the animal findings for human behavioral control must be scrutinized. Indeed, it has been argued recently that rodent models of the shift of behavioral control related to drugs of abuse has exclusively examined habitization of reward-seeking behavior and neither habitual drug intake nor avoidance of aversive states (McKim, Shnitko, et al., 2016). This is an unfortunate shortcoming as the habitization of drug consumption is a crucial assumption of the learning account by Everitt and Robbins (2016) and other dual-system approaches and the avoidance of aversive states (e.g. withdrawal symptoms) has often been associated with SUDs (Koob, 2013; Koob & Le Moal, 2001). Additionally, avoidance behavior has been shown to shift from goal-directed to habitual faster in obsessive-compulsive disorder patients than in control participants (Gillan et al., 2014), which is of interest because obsessive-compulsive disorder

has been shown to have many similarities with SUDs (Fontenelle, Oostermeijer, Harrison, Pantelis, & Yücel, 2011). Furthermore, human frontal cortical areas have expanded severely during evolution and this difference to the relative volume of rodent cortical areas might very well limit the comparability of rodent and human research (McKim, Shnitko, et al., 2016), especially regarding higher cognitive functions like goal-directed behavioral control that strongly depends on frontal cortical areas (Dolan & Dayan, 2013). Thus, the animal research that gave rise to Everitt and Robbins' (2016) learning account needs to be extended to scrutinize its fundamental role for models of human SUDs, but the concerns not yet justify abandoning this theoretical approach altogether.

Alternatively, the learning theory (Everitt & Robbins, 2016) could be modified instead of refuted. The most parsimonious alteration of the underlying theoretical model in consequence to our results would be to limit the assumed generalization of the shift in behavioral control beyond alcohol use. Indeed, while the evidence for a diminishment of goal-directed control in reward-seeking behavior by alcohol consumption in procedures with alcohol outcomes is quite strong in the rodent literature (Corbit, Nie, & Janak, 2014; Dickinson et al., 2002; Lopez, Becker, & Chandler, 2014; Mangieri, Cofresí, & Gonzales, 2012; Samson et al., 2004), the evidence for generalized, outcome-unspecific effects of alcohol intake is still sparse (Corbit et al., 2012). Moreover, it seems plausible that actual alcohol consumption in human AUD would be at least partially stimulus-evoked due to increased salience of alcohol cues on the one hand (as revealed by increased alcohol cue reactivity in AUD patients compared to healthy controls; Schacht, Anton, & Myrick, 2013) and automatic alcohol intake elicited by alcohol stimuli in AUD after numerous repetitions of this behavioral program on the other. However, empirical evidence for this habitual drug intake is still missing in the human domain. Yet, there is one descriptive finding in our AUD patient sample that hinted at a shift of control over alcohol intake from goal-directed to habitual. Interestingly, some of the AUD patients yielded the high score in the AEQ. Alcohol use disorder patients' AEQ scores were significantly higher than those of the control group. Thus, patients still expected numerous positive consequences of alcohol consumption even after years of chronic alcohol use (one inclusion criterion was an AUD diagnosis for at least three years) and a degree of impairment in their personal, social, and work life that had led them to seeking treatment on average four times before the current treatment. This persistent positive expectancy might indicate that there is no re-learning of the value of alcohol-use options in AUD, although alcohol use will probably have had adverse consequences. If indeed AUD patients in our sample experience negative effects of alcohol intake but nevertheless do

not adapt their value expectation, this indicates habitual alcohol intake in real-life scenarios in AUD. Yet, as mentioned previously, this issue awaits empirical investigation.

The third possibility to resolve the incompatibility of our results with the learning account (Everitt & Robbins, 2016) is an extension of the theory in terms of a search for meaningful subgroups or endophenotypes (Gottesman & Gould, 2003) for which this (possibly generalized) transition in control strategies is or is not an important factor in the development and maintenance of AUD (Everitt & Robbins, 2016). As was the main insight from the UFA (Redish et al., 2008), the paths to an SUD can be diverse and not all AUD patients need to be affected by an imbalance in control strategies. There is heterogeneity in the clinical population of AUD patients, let alone SUD patients in general, so that investigation into consistent clusters of underlying features may yield valuable advances for understanding the mechanisms behind this class of disorders. The spectrum of inhibitory control and its underlying genetic and epigenetic determinators might be one promising aspect of such an endophenotype for SUDs in general (Ersche et al., 2012, 2013), especially because of inhibition's fundamental role in enabling goal-directed behavior (Diamond, 2013), its established diminishment in SUDs (Copersino, 2017; Everitt & Robbins, 2016), and its relevance for successful treatment of SUDs (Konova, Moeller, & Goldstein, 2013; Zilverstand, Parvaz, Moeller, & Goldstein, 2016). Without proper inhibition of irrelevant or inadequate thoughts, memories, perceptions, emotions, and behavioral responses, achievement of any long-term goal is almost impossible or at least very challenging. Moreover, failed behavioral inhibition has been suggested to result in impulsive or compulsive behavior and delay and probability discounting have been described as sub-processes of behavioral inhibition (Bari & Robbins, 2013; Diamond, 2013). As we have shown in Study 3, delay and probability discounting were altered in AUD patients compared to control participants making their choice patterns more impulsive. However, as can be seen in Figure 11, not all patients had comparably low values in these parameters. These behavioral paradigms reveal substantial interindividual differences in VBDM even within the group of AUD patients. This variance in discounting processes in particular, and in inhibitory control in general, might be decomposed into subgroups with methods of dimension reduction (e.g. factor analysis, structural equation modeling) or clustering algorithms (e.g. latent class analysis). But to do so, a large amount of data for each participant is needed covering a wide range of distinct yet connected constructs. Hence, the rich data set acquired by our research group might deliver insights in this regard in the near future.

In summary, our findings indicate no general shift from goal-directed to habitual control in AUD or in association with levels of non-pathological alcohol use. Findings in rodent models of drug use as well as studies in human SUD patients need to be extended to examine the habitization of actual drug consumption. If evidence for this shift of control regarding the consumption of the abused drug is found, the generalization of this shift of control to other non-drug-related areas could be investigated in a second step. Thus far, Everitt and Robbins' (2016) learning account is not supported by our and previous findings, at least for AUD.

5.1.2 Neuroimaging correlates of goal-directed and habitual control

Neuroimaging analyses replicated the findings of Daw et al. (2011) in the young adults of Sample 1 and the AUD patients and controls of Sample 2. Model-free RPEs as well as the model-based signature in this reinforcement learning signal were associated with BOLD responses in ventral striatum and vmPFC. This replication showed that the original effect of shared neural resources between the goal-directed and habitual system was present in a sample much larger than in the original study (Daw et al., 2011; N = 17) and in healthy participants as well as persons suffering from AUD. However, the magnitude of these BOLD responses were not related to alcohol use measures in Sample 1 and AUD status in Sample 2 except for an exploratory finding of an increased association of BOLD responses to model-free RPEs in putamen with earlier onset of drinking in the young-adult sample and a decreased model-based signature in vmPFC in relapsing patients compared to abstainers and control participants. These two findings seem plausible in themselves: during the transfer from goal-directed to habitual control, the focus of neural activation controlling behavior is supposed to shift from ventral to dorsal striatum (Everitt & Robbins, 2005, 2016) and the activation of vmPFC (Volkow & Baler, 2014) and its influence on striatal activation supposedly decreases (Everitt & Robbins, 2005, 2016). Furthermore, decreased vmPFC activation in relapsers was accompanied by decreased grey matter density in vmPFC (see Table S 13). Therefore, relapsing AUD patients seemed to have neuroanatomical changes in line with previous reports (Beck et al., 2012; Durazzo et al., 2011), but they did not translate to altered behavioral strategies in the Two-Step task.

However, the learning account of SUDs (Everitt & Robbins, 2016) would have predicted more general alterations in neural activation in dependence to the amount and history of alcohol misuse. The emerging imbalance between excitatory D1 and inhibitory D2 signaling in striatum after chronic alcohol misuse should have led to decreased prefrontal

activation and, in turn, decreased prefrontal modulation of striatal activation, possibly contributing to impulsive and habitual decision making (Volkow & Baler, 2014). In line with this model, we did find increased impulsive choice behavior in AUD patients in Study 3 and reduced model-based BOLD responses in the vmPFC of prospective relapsers in Study 2, but no generally increased habitual strategies in the patient sample in the Two-Step task. However, the lack of a neural difference between patients and controls in Study 2 complemented the missing finding in a behavioral level. This might again advocate for subgroups within the population of AUD patients or an alcohol-specific instead of outcome-unspecific shift in control strategies.

5.1.3 Modulators of the valuation systems and alcohol use (disorders)

Our findings in Study 3 indicate an involvement of impulsive choice regarding delays, risks, and valence of options in AUD but not non-pathological alcohol use. This is partly consistent with previous studies suggesting increased impulsivity to be involved in the development and maintenance of SUDs (Bickel et al., 2007; Dalley et al., 2011; Kreek, Nielsen, Butelman, & LaForge, 2005; Stanford et al., 2009). Our results regarding lower loss aversion and stronger delay discounting and risk taking regarding monetary gains in AUD patients complement this line of research and fit well with the assumed increased impulsive choice behavior in AUD. Furthermore, the lack of consistent intercorrelations among the four paradigms used in Study 3 corroborates the suggestion of multiple impulsivities (Green & Myerson, 2013). These authors showed that delay and probability discounting might be separate and partly independent dimensions of impulsivity. Our findings support this view and extend it with the dimension of the valence of outcomes. Thus, persons might differ in their appraisal of delay, risk, and valence and might be grouped regarding specific patterns when combining their attitudes toward these three dimensions. The resulting subgroups could all show the same pathologies, but the underlying mechanisms leading to the individual syndrome could differ between the subgroups. This is in line with the assumptions of the UFA (Redish et al., 2008) that the same class of disorder might entail individuals with very different etiological paths.

In addition, the finding of lower risk seeking facing monetary losses added a new perspective on choice biases in AUD patients showing that it might have been a general tendency to overestimate the probability of uncertain outcomes instead of or besides a general disregard for the risk of an option. This general choice bias regarding stochastic events is

understudied in AUD patients. It holds promise to yield further insights into the mechanisms of AUD given its shown association to treatment outcome in AUD patients, but further research is needed to corroborate this finding first.

Finally, we did not find evidence for increased impulsive choice to be a predisposing risk factor of non-pathological alcohol consumption. This is at odds with the tentative suggestions of an impulsive endophenotype (Dalley et al., 2011) and possible common genetic factors for delay discounting and AUD (Mitchell, 2011). The ongoing assessment of the young-adult sample will provide further insights whether baseline VBDM parameters might predict escalation of drinking behavior, but so far our results do not indicate a considerable role as a risk factor for alcohol use per se.

5.1.4 Integration of findings

These findings indicate that AUD patients do not have deficits in higher-order cognitive processes like goal-directed control of behavior, but in processes on a lower level. In their model of VBDM, Rangel, Camerer, and Montague (2008) have suggested that processing features like delay and risk of outcomes are lower-order processes being implemented in the habitual, goal-directed, and Pavlovian valuation systems. Thus, it is possible that AUD patients have a different way of integrating these features in the subjective value of one option, but not in the general valuation schemes in the higher-order goal-directed, habitual, and Pavlovian valuation systems. If this assumption was true, we could reveal differences in goal-directed and habitual control between pathological and healthy populations only in tasks, in which these modulating features have a palpable influence on the computed subjective values. This is not the case in the Two-Step task. The delay until the outcome is constantly below two seconds and, therefore, almost irrelevant. The valence of the outcome is either positive or zero diminishing the influence of loss aversion. Only the probability of reward receipt (i.e. the risk of options) is varying during the task and should exert influence on the valuation systems. Yet, it is unclear how the on average more risk-taking choice strategies of AUD patients would translate to Two-Step task performance. The design of this task makes it difficult for the participants to derive the actual risk of one option (see section 5.2.1). Thus, the perceived risk will probably not differ strongly between the different 2nd-stage options, thereby decreasing the influence of risk appraisal on option valuation. Consequently, additional analyses revealed no significant associations between measures of model-free and model-based control in the young-adult sample with the four VBDM parameters (all

Spearman's $\rho < |.142|$, all ps $> .061$; Table S 17, Appendix D). This is in line with one recent report for delay discounting (Solway, Lohrenz, & Montague, 2017) and is the first reported finding in this vein for the other three VBDM parameters.

In summary, while lower-order cognitive functions showed systematic alterations in AUD, higher-order functions did not, and neither were associated with non-pathological alcohol use.

5.2 Limitations

There are limitations to our results that need to be kept in mind when interpreting these findings. First, the observation period of the young-adult sample (Sample 1) was rather short. This impedes the interpretation of the longitudinal analyses in Study 1 and 3. Further observation will show how many of the participants of Sample 1 will show escalating drinking behavior and whether our measures of VBDM might predict the transition from non-pathological social to pathological alcohol consumption. Second, there was a selection bias in sampling these participants. Registration offices sampled 18-year-old men randomly but those who responded and committed themselves to our study were more frequently pupils attending academic high school (German "Gymnasium") than what is observed in the general population of this age (65.8% of our sample compared to 51.3% on average in Saxony and Berlin; Autorengruppe Bildungsberichterstattung, 2016). Despite this selection bias, there were neither ceiling effects in the assessment of working memory capacity nor deviations from the general population in measures of processing speed and verbal intelligence in this sample. Thus, task performance should not have been systematically changed due to the overrepresentation of participants with a higher educational background. However, it is possible that drinking patterns over the whole group would have shown more variance if we would have sampled relatively fewer participants with a rather high educational background. This selection bias might have led to an underestimation of correlative associations. Third, young-adult participants were all male. We followed this sampling approach, because men have a three times higher risk for the development of AUD than women (Wittchen et al., 2011) making it more probable to have included participants with escalating drinking patterns during the observation period, but this also reduces the scope of generalizability of our findings to men only.

Furthermore, our exclusion criteria for the AUD patients in Sample 2 contained comorbid mental and neurological diseases. On the one hand, this led to a sample in which

alterations are more probably associated with AUD itself than with concomitants like Major Depression, Korsakoff's syndrome, or personality disorders. On the other hand, this patient sample is thus less representative for AUD patients in general as epidemiologic studies have shown that of those AUD patients who seek treatment 41%, 33%, and 33% have also suffered from an independent comorbid mood, anxiety, or substance use disorder, respectively, in the past 12 months (Grant et al., 2004). For the aim of this thesis, this sampling procedure was adequate, because it enabled us to examine effects specific to AUD. However, the generalizability of our findings to the population of all treatment-seeking AUD patients is impeded as a consequence. In addition to these limitations, there are methodological limitations due to the task design of Two-Step.

5.2.1 Methodological critique of the Two-Step task

With its elaborated design and sophisticated computational model of task performance, the sequential decision-making task designed by Daw et al. (2011) tried to solve the difficulties in operationalizing goal-directed and habitual control in human research (see section 1.2.3.2). However, there is accumulating evidence that the interpretation of findings using the original Two-Step task might be more challenging than previously thought (Akam, Costa, & Dayan, 2015; Kool, Cushman, & Gershman, 2016; Kool, Gershman, & Cushman, 2017; Toyama, Katahira, & Ohira, 2017). Recent theoretical advances underpinned with simulations and empirical data showed that model-based behavioral strategies in the Two-Step task do not lead to increased reward rates for participants, in turn decreasing the motivation to invest the mental effort to behave goal-directedly (Akam et al., 2015; Kool et al., 2016). This might be due to the relative difficulty of distinguishing high from low reward probability options on the second stage of the Two-Step task due to the limited information entailed in the dichotomous outcomes of 2nd-stage choices (rewarded vs. unrewarded) and, thus, the limited insight in what the best stimulus might be at present. After all, one can only sample reward information from one 2nd-stage stimulus at a time and needs several repetitions to deduce the corresponding reward probability for this stimulus, and all the while the reward probabilities for the other three 2nd-stage stimuli change unobserved. Therefore, a model-based strategy has decreased importance at 1st-stage choice. This is worsened by the rather small differences in reward probabilities between options at 2nd stage resulting from the reflecting boundaries of the Gaussian random walks at 0.25 and 0.75. As a result of these boundaries, two different 2nd-stage stimuli can have a maximum difference in reward

probability of 50% when one is at the top and the other at the bottom of the possible probability distribution, but on average the winning probability of two 2nd-stage stimuli differs by only 18% (Kool et al., 2016). Another potential disadvantage of the currently used setup of the Two-Step task is that the rare transitions lead to a decrease in the accuracy-effort association, because model-based control at the 1st stage might not end up in the desired state on the 2nd stage. Consequently, investing mental effort to exert model-based control was not associated with increased accuracy of performance and more reward (Kool et al., 2016), thus, frustrating the participant and further decreasing the motivation to invest effort. Taken together, though the Two-Step task might be well designed to measure the balance between model-free and model-based strategies in theory, participants have no incentive to exert goal-directed control over their behavior due to the task setup. This issue confounds the previously obtained results as it is not apparent whether the individually estimated amount of goal-directed control indeed corresponds to the ability of the participant or rather is a result of demotivation (which would even be cost efficient given the lack of benefit from investing cognitive effort). I have performed several additional analyses to test the influence of these shortcomings of the task design in our samples.

5.2.1.1 Additional analyses – Goal-directed control, motivation, reward, and cognitive abilities

First, we asked the participants to rate their motivation to choose the currently best stimulus in the Two-Step task and how this motivation changed over the course of the experiment right after they performed the task paradigm (Figure 13, left panel). These ratings revealed that participants on average reported to be rather motivated during task performance (Mdn = 5, mode = 6 on a scale ranging from 1 = *little motivated* to 7 = *very motivated*), but motivation decreased on average over the course of the task (Mdn/mode = -1 on a scale ranging from -3 = *decreased* to 3 = *increased*). Furthermore, ratings of motivation correlated positively with parameters of model-based control (MB_{score}; Spearman's $\rho = .153$, $p = .037$) but the change of motivation did not (see Figure 13, right panel). As you can see in the upper right panel of Figure 13, every participant in the highest 15% of model-based behavior ($MB_{score} > 0.59$, vertical line) was motivated to perform well (motivation rating ≥ 5).

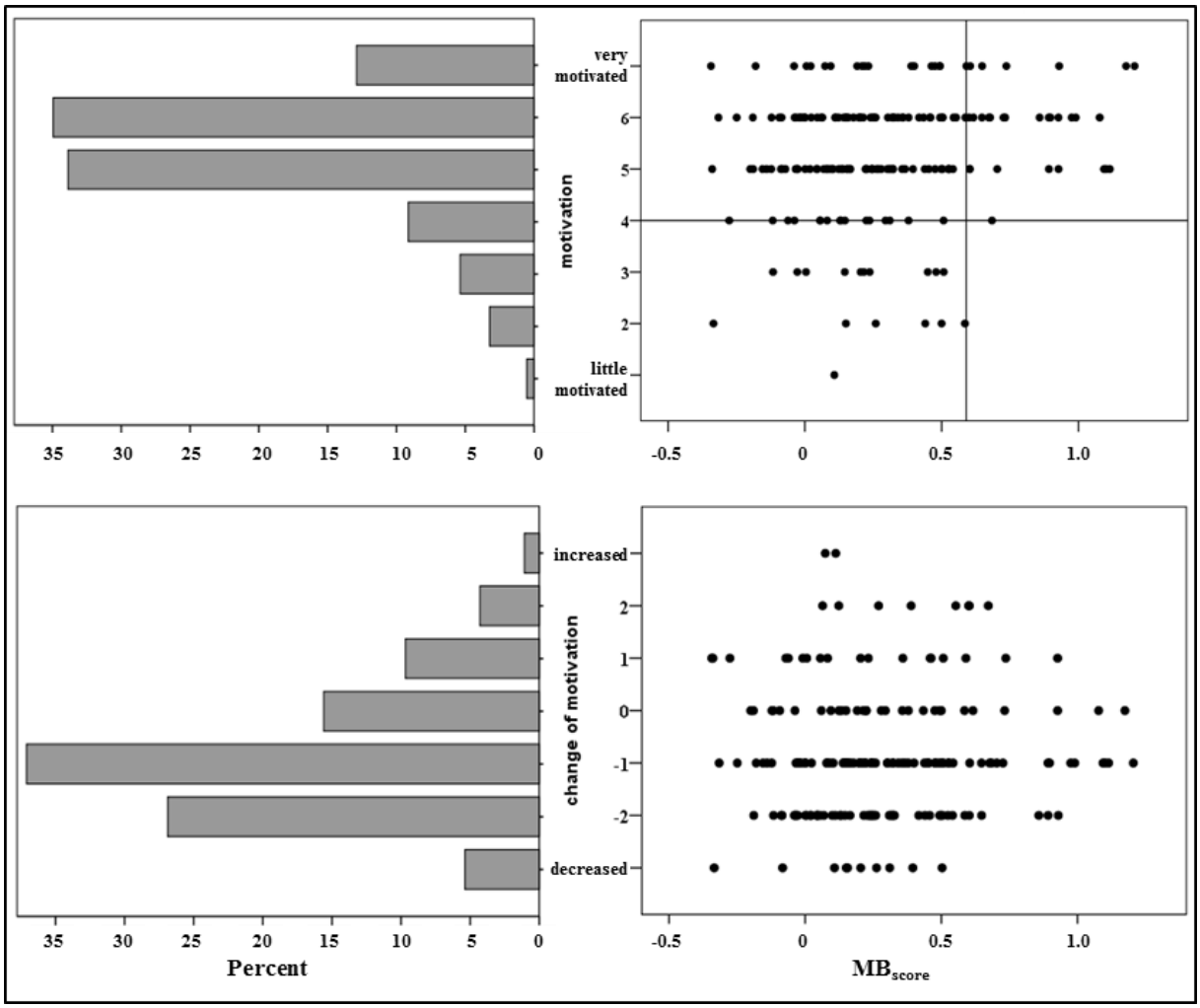

Figure 13. Upper panel: Histogram of Sample 1 participants' answers to rate their motivation to choose the currently best stimulus in the Two-Step task on a seven-point Likert scale (left) and the correlation of this rating with the score for model-based control strategies derived from the individual stay probabilities (MB_{score}; Spearman's ρ=.153, p=.037). The horizontal line in correlation plot represents the middle category of the Likert scale, the vertical line represents 85th percentile (MB_{score} = 0.59). Lower panel: The same as in the upper panel but with participants' ratings of how their motivation has changed during task performance (Spearman's ρ=.053, p=.474; N=186 for both panels due to two missing data points in the ratings).

Although this is speculative and exploratory, this correlational pattern suggests that there might be three subgroups in this sample regarding their Two-Step behavior: one group being motivated and exerting goal-directed control although it is not profitable (upper right quadrant in correlation plot, corresponding to 15% of the sample), one group lacking motivation and ranging from low to medium goal-directed control (lower left quadrant in correlation plot, corresponding to 9% of the sample), and one group being motivated to perform well but nevertheless yielding a rather wide range of the amount of goal-directed control (upper left quadrant in correlation plot). Thus, the motivation to perform well in the Two-Step task in this sample seems to be a necessary but not sufficient condition for high amounts of goal-directed behavior, but reported motivation cannot explain low to medium amounts of goal-directed control. In general, this shows that motivation was not decreased in

most of our participants and the amount of goal-directed control varied widely. Additionally, motivation to perform well in the task was similarly distributed in AUD patients (Mdn = 6, mode = 6) and control participants of Sample 2 (Mdn = 5, mode = 6), and did not differ between these two groups (z = -1.35, p = .179 [4]). These additional findings do not invalidate the critique on the Two-Step task, but indicate that our results might not have resulted from pure demotivation of the participants.

Moreover, Kool, Cushman, and Gershman (2016) found no association between the degree of goal-directed control and the average reward rate in the Two-Step task. This finding is evident in our young-adult sample, too (MB_{score} x average reward rate; Spearman's ρ = .016, p = .832). Nevertheless, participants' 2nd-stage choice behavior was not random. The four 2nd-stage stimuli can be brought into an order from the lowest to the highest reward probability associated with them at each trial for each participant and ranked accordingly (from 1 = lowest to 4 = highest probability). With the help of this coding scheme, I could classify each choice depending on its relative optimality and calculate a rank sum score of this choice parameter. By dividing this rank sum by the amount of trials (201 minus missing trials), I obtained the average rank of the chosen 2nd-stage stimuli. Examining this rank score yielded two important insights: first, the average reward score over the group differed significantly from 2.5, which would have signified random choice behavior on 2nd stage (t(187) = 17.30, p < .001; see Figure 14, left panel). Second, the amount of model-based control during the Two-Step task correlated positively with the average rank of chosen stimuli (Spearman's ρ = .171, p = .019). These analyses replicate the finding of Kool, Cushman, and Gershman (2016) that goal-directed behavior in the original Two-Step task does not benefit the participant in terms of an overall increased reward rate. However, they also suggest that participants in our samples tried to perform well despite the lack of benefit from exerting mental effort, again suggesting that task performance was not just a result of demotivation or random choice behavior.

A third approach to put the validity of our Two-Step findings to the test is by looking at the association with cognitive abilities. Previous studies have found that higher working memory capacity and cognitive processing speed was related to more model-based goal-directed control in the Two-Step task (Schad et al., 2014; Smittenaar et al., 2013), though this relation might be mediated by acute (Otto, Raio, Chiang, Phelps, & Daw, 2013)and chronic stress (Friedel et al., 2017).

[4] Mann-Whitney U-test due to ordinal scale of motivation ratings.

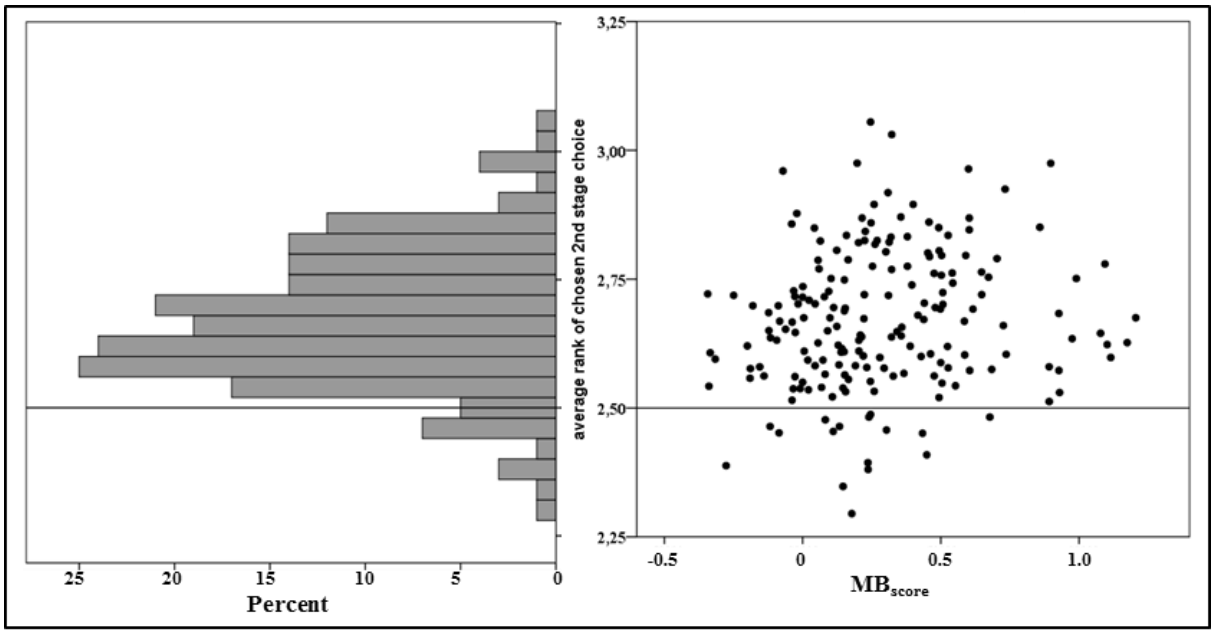

Figure 14. Display of choice behavior of young-adult sample on 2nd stage of the Two-Step task. Left panel: Histogram of the average rank score of chosen 2nd-stage stimuli. Right panel: Scatterplot of average rank score of chosen 2nd-stage stimuli and model-based control parameter calculated from stay probabilities (MB_{score}). Horizontal line in both plots at 2.5 represents theoretical random choice behavior.

Indeed, additional correlational analyses of the association between model-based control and cognitive abilities in Sample 1 revealed significant correlations of the score of model-based behavior (MB_{score}) with performance in the Trail Making Test B (TMT-B; Spearman's ρ = -.217, p = .003; Reitan, 1992), digit span backwards (DSbw; Spearman's ρ = .198, p = .006; Wechsler, 1997) and digit symbol substitution test of the Wechsler Adult Intelligence Scale (DSST; Spearman's ρ = .204, p = .005; Wechsler, 1997), and Mehrfachwahl-Wortschatztest Version B (MWT-B; Spearman's ρ = .183, p = .012; Lehrl, 2005). These correlations signify an association between more model-based behavior in the Two-Step task to be associated with faster cognitive processing speed (TMT-B, DSST), higher working memory capacity (DSbw), and a higher proxy for verbal intelligence (MWT-B). Taking together the results of these additional analyses indicated that the amount of goal-directed and habitual control utilized in Study 1 and 2 represented the actual abilities of the participants at least in part, which suggests our results might not be invalidated by the methodological critique of the Two-Step task. But at the same time, the associations of Two-Step task performance with individual cognitive abilities show the necessity to investigate this link further in health as well as their possible alteration in disease (see section 5.3.1).

5.3 Outlook for future studies

Despite the indication that the design shortcomings of the original task version (Daw et al., 2011) might not have solely driven our results, changes of the experimental paradigm should be considered for future research. Especially the task version by Kool and colleagues (Kool et al., 2016) holds promise as they have shown the superiority of the adapted paradigm and analyses in finding evidence for model-based goal-directed behavior in simulations as well as participant data (Kool et al., 2016; Kool et al., 2017). In their task version, there are two different possible states at 1st stage. Each 1st-stage state entails two stimuli to choose from. Choice of one stimulus will deterministically lead to one 2nd-stage stimulus and choice of the alternative stimulus to the other one. At 2nd stage, there is no more choice involved as there is only one stimulus presented, which has to be selected involuntarily. After "choosing" the 2nd-stage stimulus, the participant earns reward in the form of points, ranging from 0 to 9, instead of a dichotomous outcome. The amount of points earned at 2nd stage varies independently for both stimuli according to Gaussian random walks with a higher drift rate than in the original version (Daw et al., 2011), so participants can directly experience changes in these probabilities. In addition, the absence of rare transitions allows them to generalize their experience from a trial starting in one 1st-stage state to the other one. This is supposed to increase the accuracy-effort association (Kool et al., 2016). Using this task version, Kool, Gershman, and Cushman (2017) could show that goal-directed control was only exerted when weighing the costs of investing mental effort against the benefits in terms of accrued rewards yielded a favorable ratio. Their new design of the Two-Step task (Kool et al., 2016) had this quality and should, therefore, be preferred over the original task by Daw et al. (2011) in designing future studies. As I cannot conclusively rule out the possibility that our null results in both samples might at least in part be due to these design issues, the finding of a lack of a generalized, outcome-unspecific shift from goal-directed to habitual control in AUD should be replicated using the revised Two-Step task to validate our findings. Additionally, the combination of our findings in all three studies with the presented limitations leads to several more suggestions for future studies.

First, the habitization of alcohol intake in persons suffering from AUD should be investigated. This is a crucial piece of information that is assumed by theories of AUD development and maintenance, but has not been investigated in the human domain, yet. To investigate this, a specific cohort of non-treatment seeking persons suffering from AUD would be needed, because working with real alcohol outcomes in treated AUD patients aiming for abstinence from alcohol would hazard treatment success and, thus, be unethical.

Future studies with this special cohort might inform theories about the alcohol-specific habitization of behavioral control. To test whether alcohol intake in persons suffering from AUD is habitual in real life, experience sampling approaches could be used. With this approach, participants' decision making regarding alcohol intake could be sampled directly in their natural environment and during every-day life, for example by using a smartphone application asking about a person's intentions of alcohol consumption several times a day and the actual amount of consumed alcohol on the day before. But it could also go beyond the mere amount of consumed alcohol to repeated, habitual tendencies to go and open the fridge looking for alcoholic beverages or to habitually go to bars without the explicit intention to do so. In addition, information about every-day behavior other than alcohol consumption could be gathered by experience sampling methods, thereby testing the assumed generalized shift from goal-directed to habitual decision-making. These possible avenues to test the alcohol-specific and outcome-unspecific habitization of decision making would complement the previous findings, which currently do not support a generalized, outcome-unspecific shift in behavioral control in AUD.

Second, habitization of alcohol consumption as well as in non-alcohol-related behavior as predictor of the transition from non-pathological to escalating, pathological alcohol use should be examined. Only the longitudinal investigation of participants traversing from non-pathological to pathological alcohol intake could yield definitive insights into etiological mechanisms. This might be possible to achieve in the ongoing investigation of the young-adult sample presented in this thesis, which will be followed-up for at least five years.

Third, big-data approaches should be utilized to search for meaningful subgroups within the cohort of AUD patients. This cohort comprises considerable heterogeneity of the afflicted persons regarding the severity of symptoms, factors contributing to chronic pathological alcohol use, comorbid mental and physical syndromes, and the areas of every-day life being compromised by the consequences of drug use (Redish et al., 2008). If future research could identify consistent patterns in the features of this clinical population, we could focus on finding the most efficient treatment plan for each AUD subtype. Finding ways to improve long-term treatment outcomes would be a very valuable endeavor seeing that relapse rates after completion of current standard detoxification treatments are often higher than 50% within the next 12 to 24 months (Stock, 2017). To aid future investigations of mechanisms involved in the etiology of AUD, possible AUD subgroups, and promising treatment approaches, a holistic, heuristic model might be of use. This model should try to integrate the insights from various streams of research into the basis of out-of-control alcohol drinking.

5.3.1 Tentative framework for future studies

Bringing together higher cognitive functions like goal-directed planning and more basic executive functions is the theme of a different line of research that attempted to draw a more nuanced cognitive model of addiction. This research line recently cumulated in Copersino (2017) sketching a dual-system model of the cognitive mechanisms of SUDs. He separated implicit, automatic, effortless processes from explicit, effortful cognitive processes (see Figure 15). The implicit cognitive processes entail classical and operant conditioning, upon which processes like cognitive biases, cue reactivity, Pavlovian-instrumental transfer, and incentive sensitization are based. The explicit cognitive processes are divided into executive functions, which Copersino defined as "mental operations necessary for the planning, execution, and monitoring of goal-directed behavior" (Copersino, 2017, p. 94), and metacognition, "the critical awareness, knowledge and control of our own cognitive processes, reasoning and decision-making" (Copersino, 2017, p. 93). The author described the etiology of SUDs as a mixture of increasing habits and urges to use a substance (strengthening of implicit processes) while contemporaneously decreasing executive functioning to counter habits and urges as well as metacognition regarding the growing number of triggers for them (weakening of explicit processes). Thus, the basic mechanism proposed by Copersino (2017) is the same as in the learning account by Everitt and Robbins (2016) and also parts of the UFA (Redish et al., 2008). However, while Everitt and Robins (2016) focused more strongly on the neural underpinnings of this mechanism and based their theory mostly on animal models of addiction, Copersino (2017) preferentially addressed the human cognitive functions and abilities underlying habitual and goal-directed control (Figure 15). Therefore, Copersino's model opens up additional avenues of research into the cognitive epiphenomena producing or accompanying the shift from goal-directed (i.e. in Copersino's terms the successful deployment of executive functions to limit or avoid substance use despite possible urges and habits of use) to habitual (i.e. the successful interference of automatic habits and Pavlovian associations with metacognition and executive functions to initiate and maintain substance use) control in SUDs.

The taxonomy put together by Copersino (2017) can be used to explore how processes underlying goal-directed and habitual control differ between the AUD patients and control participants of Sample 2, which did not differ in general in model-free and model-based control in the Two-Step task (Study 2). One of the epiphenomena predicted by the strengthening of implicit cognitive processes is the growing influence of Pavlovian conditioned stimuli on instrumental behavior (i.e. Pavlovian-instrumental transfer, PIT;

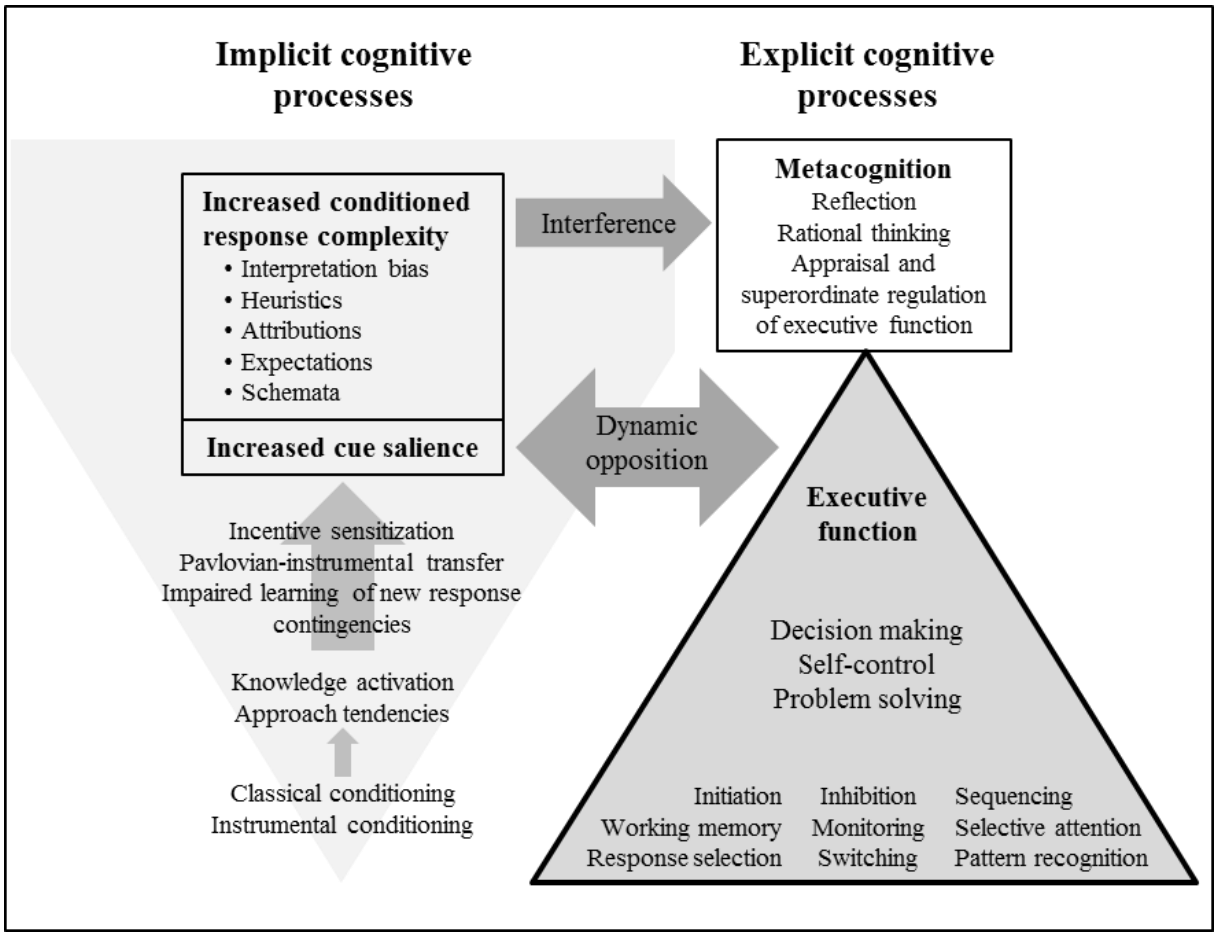

Figure 15. Schema of the model of cognitive processes involved in the development and maintenance of SUDs (adapted from Copersino, 2017).

Cartoni, Balleine, & Baldassarre, 2016; Estes, 1948). Pavlovian-instrumental transfer has previously been assumed to be one factor underlying maintenance of and relapse to AUD (Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009) and, indeed, we showed stronger behavioral PIT effects in AUD patients compared to control participants in a pilot study (Garbusow et al., 2014) and in Sample 2 (Garbusow et al., 2015; Sommer et al., 2017). Moreover, we could previously show in the young adults of Sample 1 and the control participants of Sample 2 that increased PIT effects were related to diminished goal-directed control in the Two-Step task (Sebold et al., 2016), which further corroborates Copersino's (2017) theoretical framework. Furthermore, Copersino (2017) related weakened executive functions with SUDs. This includes diminished working memory capacity, which has previously been found to be decreased in AUD patients (see meta-analysis by Stavro, Pelletier, & Potvin, 2013) and is also lower in the patients of Sample 2 compared to the

control participants (DSbw, z = -3.97, p < .001 [5]), although we successfully matched patients and controls for years of school education and age. In addition, decreased executive function entails increased impulsivity and delay discounting (Copersino, 2017; Diamond, 2013; N. P. Friedman & Miyake, 2016), which have often been shown to be related to AUD (Bickel et al., 2014; Stanford et al., 2009; Laura Stevens et al., 2014) and were also increased in our patient sample compared to the control group (Study 3, Table 7; BIS-15: $t(201)$ = -2.76, p = .006; DD: z = -3.15, p = .002 [5]). In summary, those processes underlying goal-directed and habitual control that we examined in Sample 2 in addition to the Two-Step task all point to diminished explicit, goal-directed and enhanced implicit, habitual control. Yet, the direct examination of these control strategies did not yield the expected group difference, which might be confounded by the task design that does not benefit those who exert goal-directed control as I have discussed previously (see section 5.2.1.).

Crucially, if we had found a systematic diminishment of goal-directed control in favor of habitual strategies, how would this have informed improving therapeutic approaches? Recently, a departure from treatment approaches trying to enhance goal-directed control in AUD patients and instead focusing on implicit processes via cognitive and attentional bias modification and habit reversal therapy has been suggested (Gladwin, Wiers, & Wiers, 2017; Stock, 2017; Wiers et al., 2011). This suggestion was based on the observation that habitual control is intact in AUD patients, whereas goal-directed control is assumed to be disrupted. Conclusive evidence for this disruption is yet missing, but even if it were to be found, the question of the cause of diminished goal-directed control would still be open. Human real-life goal-directed control is embedded in an ever-changing world with an extremely large state space (Gershman & Daw, 2017). Finding a beneficial path through this state space and navigating to an attractive long-term goal, that is, controlling your behavior in a goal-directed manner, requires cognitive resources and proper executive functioning (Copersino, 2017; Otto et al., 2013; Schad et al., 2014; Smittenaar et al., 2013). Deficits in a task of goal-directed control like devaluation or sequential decision-making paradigms would not yield information about the cause of decreased goal-directed behavior. These deficits could be due to decreased working memory capacity interfering with maintaining the currently pursued goal, or decreased inhibitory control allowing intrusive stimulus-response habits to take control over behavior or task-irrelevant information to capture attention among other things.

[5] Mann-Whitney U-test due to violation of normality assumption of this measure.

To disentangle these interrelated constructs, future studies would need to acquire large data sets in large samples[6] of AUD patients and healthy control participants. This big data approach is probably only to be accomplished by collaborative efforts of several research groups at various sites and the adoption of open science practices. Furthermore, the data should include a big variety of measures on alcohol use patterns, executive functions, metacognition, habitization of alcohol use and non-alcohol-related behavior, impulsivity, and intelligence. The primary ideas behind the use of big data approaches in such a wide heuristic model of interrelated constructs to guide future research are the following. First, there has been a divide between clinical psychology/psychiatry research and cognitive psychology/neuroscience in investigating cognitive approaches in psychopathology leading to decreased communication between fields examining the same processes. That is why theoretical and methodological advances in one of those fields were often not applied in the other (Snyder, Miyake, & Hankin, 2015). Consequently, future clinical studies should begin with holistic models of psychological function from basic research and seek to advance understanding of these mechanisms in disease. Second, the amount of studies examining single impaired mental processes in single mental disorders is overwhelmingly large by now. Significant scientific progress is probably not to be expected from future studies taking the same route (McTeague, Goodkind, & Etkin, 2016). Rather, meta-analyses are needed to combine the findings of previous studies, which have higher statistical power and yield more stable results than single clinical studies with often rather small sample sizes, especially in clinical neuroscience studies. The results of these meta-analyses can then inform the heuristic models in turn. Third, there should be efforts made to conduct studies using more than one task paradigm or questionnaire per latent construct, although this is less ecological. As Harden et al. (2017) have recently shown in a sample of more than 800 adolescent twins, no single behavioral task of reward seeking or cognitive control (including a delay discounting task and Iowa Gambling Task) sufficed to operationalize the underlying construct as most variance in the performance of one task was task-specific and non-systematic for the construct. This finding strongly advocates for the use of several tasks and combining their results in investigating rather complex constructs and, thus, supports the notion of task diversity even at higher costs for data acquisition. Factor analytic and structural equation modelling approaches are ideal candidates for this endeavor. The research group "Learning

[6] The actually needed sample size depends on many variables besides the desired power for a given effect size and level of α. For structural equation models, the number of factors, the expected factor loadings, and percentage of missing data also play a role (see Wolf, Harrington, Clark, & Miller, 2013).

and Habitization as Predictors of the Development and Maintenance of Alcoholism", within which the presented data were acquired, represents a step in the right direction but could only cover a limited area of the processes and mechanisms associated with non-pathological and pathological alcohol use. Finally, computational modeling will be vital in bridging the gap between behavioral and neuroscientific approaches (e.g. Huys, Maia, & Frank, 2016; Teufel & Fletcher, 2016). This forces the researcher to formalize the assumed cognitive processes in an algorithmic way leading to increased precision and better communicability of research. Furthermore, analyses on this level have the potential to overcome descriptive and correlational models and yield evidence of causal relationships between neural and behavioral data. It is also a useful tool in translating behavioral findings to neuroimaging data and might help identify transdiagnostic features of perception, decision making, and behavior.

5.4 Conclusions

This thesis has made a valuable contribution to understanding the cognitive mechanisms of alcohol use and AUD. I have shown that processes of VBDM are unlikely predisposing factors for alcohol consumption on a non-pathological level. Regarding AUD, systematic alterations of the valuation of delays, risks, and the valence of expected outcomes were evident while a general imbalance between goal-directed and habitual control was absent in the group of AUD patients. In addition, relapse to heavy drinking in detoxified AUD patients was associated with a tendency to overestimate probabilities of uncertain losses and decreased goal-directed control in those patients with high positive expectancies of alcohol consumption. Moreover, the neuroimaging analysis of these processes in both samples did not yield reliable associations with alcohol use. Taking all of these findings together, there is not much support for the learning account of SUDs (Everitt & Robbins, 2016) for alcohol, which is why I advocate for a more detailed investigation of the cognitive mechanisms involved in the development and maintenance of AUD. While our ongoing examination of the young adults of Sample 1 might deliver a better understanding of cognitive mechanisms leading to escalation of drinking behavior, future studies are needed to put our findings in the broader context of various cognitive domains related to alcohol use and AUD and find possible subgroups or endophenotypes within the heterogeneous population of persons suffering from AUD. Though these insights signify important steps towards the understanding of cognitive and neural mechanisms in AUD, we still have a very long way ahead of us until we will reach this goal.

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Appendix

A Supplementary Information of Study 1

A.1 Supplementary Methods 1 - behavioral

A.1.1 Measures of goal-directedness

In the computational modeling we exactly follow Daw *et al.* (2011). For completeness we repeat the used methods here. Two states *s* that are visited during trial *t* are denoted $s_{x,t}$, where the index *x* indicates the stage: $s_{1,t}$ denotes the 1st-stage state, which is always the same; $s_{21,t}$ and $s_{22,t}$ denote the two 2nd-stage states, only one of which is visited per trial. Choices $a_{x,t}$ = {1, 2} lead to transition between successive states, which are probabilistic at the 1st-stage ($a_{1,t}$) and deterministic at the second stage ($a_{2,t}$). Probabilistic 1st- and 2nd-stage rewards are denoted by $r_{1,t}$, which is always zero, and $r_{2,t}$, which can be zero or one. We used the model-free reinforcement learning algorithm SARSA(λ) temporal difference learning (Rummery & Niranjan, 1994) to model habitual choices. Here, action values $Q_{TD}(s_{x,t}, a_{x,t})$ are used to compute the reward prediction error (RPE):

(1) $$\delta_{x,t} = Q_{TD}(s_{x+1,t}, a_{x+1,t}) + r_{x,t} - Q_{TD}(s_{x,t}, a_{x,t})$$

Q_{TD} values are then updated based on the RPE via

(2) $$Q_{TD}(s_{x,t}, a_{x,t}) = Q_{TD}(s_{x,t}, a_{x,t}) + \alpha_x \delta_{x,t}$$

with free learning parameters α_x. We used separate learning rates α_1 and α_2 for 1st- and 2nd-stages. We moreover used the eligibility parameter λ (Sutton & Barto, 1998), by which 1st-stage *Q* values were updated based on 2nd-stage RPE via

(3) $$Q_{TD}(s_{1,t}, a_{1,t}) = Q_{TD}(s_{1,t}, a_{1,t}) + \alpha_1 \lambda \delta_{2,t}$$

Critically, the habitual system only learns from the non-/rewarding consequences of actions, but does not consider the structure of the transitions between stages. The goal-directed system, to the contrary, computes 1st-stage action values $Q_{MB}(s_{1,t}, a_{1,t})$ at each trial by constructing a tree of states, actions and transitions, and by weighting each action's expected outcome by the probability of their occurrence:

(4)

$$Q_{MB}(s_{1,t}, a_{1,t}) = P(s_{21,t}|s_{1,t}, a_{1,t}) \max_a Q(s_{21,t}, a_{21,t}) + P(s_{22,t}|s_{1,t}, a_{1,t}) \max_a Q(s_{22,t}, a_{22,t})$$

Subjects were instructed that transitions between 1st and 2nd stage are probabilistic with one transition being more probable than the other. In the computational model, the more frequently observed ("common") transition was set to probability 0.7 and the other ("rare") was set to probability 0.3. Goal-directed and habitual action values were combined via weighting parameter ω:

(5) $$Q_{net}(s_{1,t}, a_{1,t}) = (1 - \omega) Q_{TD}(s_{1,t}, a_{1,t}) + \omega Q_{MB}(s_{1,t}, a_{1,t})$$

Here, the relative contribution of model-free and model-based action values is determined by the free weighting parameter ω. A parameter value of ω = 0 indicates fully model-free choice and ω = 1 indicates fully model-based choice. At 2nd-stage, *Q* values are assumed to be identical for both systems: $Q_{net}(s_{2,t}, a_{2,t}) = Q_{TD}(s_{2,t}, a_{2,t}) = Q_{MB}(s_{2,t}, a_{2,t})$. Integrated *Q* values were passed through a softmax function to compute action probabilities:

(6) $$P(a_{x,t} = a | s_{x,t}) = \frac{\exp(\beta_x [Q_{net}(s_{x,t}, a_{x,t}) + \rho\, rep(a)])}{\sum_A \exp(\beta_x [Q_{net}(s_{x,t}, A_{x,t}) + \rho\, rep(A)])}$$

Given the Q values, free inverse-temperature parameters β_x determine how noisy choices are. Choice behavior is purely random for a value of $\beta_x = 0$, always and deterministically preferring higher-valued choices for a value of $\beta_x = \infty$, and matching probability and value for an intermediate value of $\beta_x = 1$. Here, we also allowed for separate parameters for 1st and 2nd stage (β_1, β_2). Effects of 1st-stage choice repetition are implemented via the indicator variable *rep(a)*, which codes whether the current action $a_{1,t}$ has been chosen on the last trial (for $a_{1,t} = a_{1,t-1} \rightarrow rep(a) = 1$ and for $a_{1,t} \neq a_{1,t-1} \rightarrow rep(a) = 0$). For second-stage actions, the parameter ρ was set to zero. The model overall contains seven free parameters $\theta = (\beta_1, \beta_2, \alpha_1, \alpha_2, \lambda, \omega, \rho)$. For fMRI analysis, we again followed Daw et al. (2011) and computed RPEs with respect to integrated action values Q_{net}, which captures a mixture of both model-based and model-free action values:

(7) $$\delta_{net;x,t} = Q_{net}(s_{x+1,t}, a_{x+1,t}) + r_{x,t} - Q_{net}(s_{x,t}, a_{x,t})$$

This effectively defines a generalized version of Equation (1). Following Daw et al. (2011), we calculated the difference between $\delta_{net;x,t}$ computed for purely model-based ($\omega = 1$) versus purely model-free ($\omega = 0$) choice.

A.1.2 Measures of alcohol consumption

The procedure for calculating $\text{Drink}_{\text{score}}$ from the CIDI (Jacobi et al., 2013; Wittchen & Pfister, 1997) drinking measures was the following: transforming the three onset variables into timespan since 1st drink, 1st time being drunk, and 1st binge-drinking episode, so each CIDI measure of drinking behavior has the same direction (higher values indicating riskier drinking behavior); setting binge-related measures to zero for non-bingers, because zero implies the least risky drinking behavior in these variables; z-standardizing of each variable; setting missing data to zero, so they do not influence the $\text{Drink}_{\text{score}}$; summing up all variables to calculate $\text{Drink}_{\text{score}}$.

A.2 Supplementary Methods 2 - fMRI

A.2.1 Individual fMRI statistics – first-level model

We set up 1st-level statistics according to Daw et al. (2011). This included an onset regressor for 2nd stage and outcome presentation. RPE_{MF} and $\text{RPE}_{\Delta\text{MB}}$ were parametric modulators locked onto this onset regressor. The time series of these two modulators are our contrasts of interest. Furthermore, we included several nuisance and regressors of no interest. This included an onset regressor at outcome presentation to control for general differences in mean activation between choice and outcome events and an onset regressor of 1st-stage presentation. Activation at this last onset regressor was being modulated by two additional parametric modulators of no interest: $P(a_{1,t}|s_A)$ from Equation 6 "as a normalized measure of the 1st-stage action value" and "its partial derivative with respect to ω" (Daw et al., 2011; Supplement, section "fMRI analysis"). In addition, we included the six motion parameters (three translation, three rotation parameters) from the realignment of the fMRI data preprocessing to control for movement artifacts.

A.2.2 ROI masks

Masks of vmPFC and ventral striatum were taken from meta-analysis software with the search term "vmPFC" and "accumbens" (http://old.neurosynth.org/terms/ and the BrainMap database (Nielsen & Hansen, 2002)), respectively. The vmPFC mask from neurosynth.org was smoothed and parts of the ACC were removed. The mask of ventral striatum from BrainMap has been thresholded with $p>.6$. These masks have been used before (Kroemer et al., 2014). Mask images were binarized with SPM's Image Calculator. Then the NAcc mask was subtracted from vmPFC to prevent overlap.

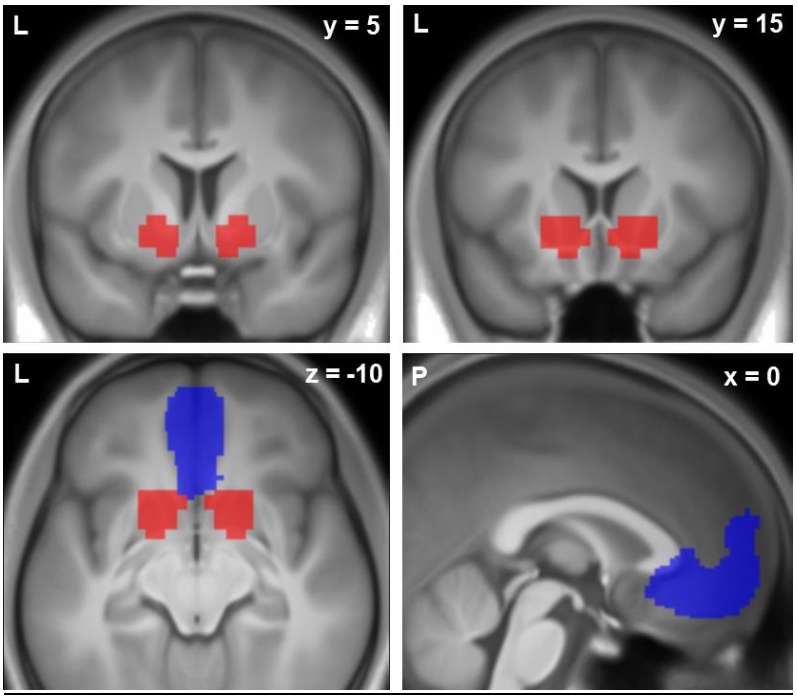

Figure S 1. ROI masks. Ventral striatum in red, vmPFC in blue.

A.3 Supplementary Results - behavioral

A.3.1 Demographics

Table S 1. Demographic information and descriptive statistics of drinking measures in the full sample (N=201).

		N	1st quartile	median	3rd quartile
Descriptive statistics of sample					
Age		201	18.24	18.33	18.50
Years in school		200	11	12	12
Measures of goal-directedness					
ω [a]		198	0.19	0.57	0.80
MF_{score}		198	-0.04	0.09	0.22
MB_{score} [a]		198	0.06	0.23	0.48
Measures of drinking behavior					
$Drink_{score}$		198	-3.80	-0.19	2.27
Age of 1st drink [a]		201	14	14	15
Age of 1st time drunk [a]		191	15	16	16
Estimated alcohol consumption in past year (g alc/day) [a]		201	3.21	7.07	16.07
Alcohol consumption in past year (g alc/drinking occasion) [a]		201	45	54	90
Age of 1st binge-drinking episode [a]		142	16	16	17
Number of binge-drinking episodes lifetime [a]		142	5	10	25
Alcohol consumption per binge-drinking episode (g alc) [a]		150	90	117	137
ADS Sum Score [a]		193	2	4	7
OCDS-G Sum Score [a]		195	1	3	5
AST (µKat/l) [a]		196	0.35	0.40	0.48
ALT (µKat/l) [a]		195	0.27	0.34	0.43
γ-GT (µKat/l) [a]		196	0.23	0.27	0.35
PEth [a]		170	10	60	60
BIS	Attention [a]	197	8	9	10
	Motor [a]	198	8	10	12
	Non-planning [a]	198	9	11	13
	Sum Score	197	27	30	34
SURPS	Anxiety sensitivity [a]	198	9	11	12
	Hopelessness [a]	198	10	12	14
	Impulsivity [a]	198	9	10	11
	Sensation seeking	197	15	16	19

[a] *Exact Kolmogorov-Smirnov test implied non-normal distribution of this measure (not tested for descriptive statistics).*
Note: N occasionally differs from 201 (or 150 in binge-drinking related measures, respectively) due to single missing data points.

A.3.2 Hierarchical logistic mixed-effects regression of 1st-stage choice repetition depending on previous trial's outcome and transition – model formula and results.

Generalized linear mixed model fit by maximum likelihood estimation, using the Laplace Approximation for integrating out individual effects. Responses (choice repetition) followed a binomial distribution and were modeled via a logistic regression model, with fixed effects predictors reward and transition in the last trial and their interaction, as well as with all fixed effects varying across subjects as random effects.

Family: binomial (logit)
Formula: repetition ~ transition * reward + (reward * transition | subject)
Factors reward and transition were effect coded (i.e. -0.5 / 0.5).
N=188

AIC	BIC	logLik	deviance	df.resid
41111.3	41230.5	-20541.7	41083.3	36703

Random effects:

Groups	Name	Std.Dev.	Corr		
sjind	(Intercept)	0.7712			
	reward1	0.3694	0.52		
	trans1	0.4090	0.30	0.22	
	reward1:trans1	1.7806	0.50	0.10	0.58

Number of obs: 36717, groups: sjind, 188

Fixed effects:

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.95779	0.05814	16.474	< 2e-16 ***
trans1	0.21745	0.04197	5.181	2.21e-07 ***
reward1	0.35805	0.04000	8.952	< 2e-16 ***
trans1:reward1	1.79721	0.14256	12.606	< 2e-16 ***

Signif. codes: $p < .05$ *, $p < .01$ **, $p < .001$ ***

Correlation of Fixed Effects:

	(Intr)	trans1	rewrd1
trans1	0.159		
reward1	0.370	0.211	
trns1:rwrd1	0.463	0.416	-0.017

To test the influence of drinking behavior on stay probabilities, we repeated the hierarchical logistic regression analysis with $Drink_{score}$ included as additional fixed between-subjects factor. Note that we had to switch optimizers to get the model to converge.

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) [glmerMod]
Family: binomial (logit)
Formula: repetition ~ transition * reward * Drink_score + (reward * transition | subject)
Factors reward and transition were effect coded (i.e. -0.5 / 0.5).
N=188

AIC	BIC	logLik	deviance	df.resid
41114.6	41267.8	-20539.3	41078.6	36699

Random effects:

Groups	Name	Std.Dev.	Corr		
sjind	(Intercept)	0.7695			
	reward	0.3648	0.52		
	trans	0.4055	0.28	0.20	
	reward:trans	1.7809	0.51	0.10	0.59

Number of obs: 36717, groups: sjind, 188

Fixed effects:

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.958004	0.058065	16.499	< 2e-16 ***
trans1	0.216141	0.041822	5.168	2.36e-07 ***
reward	0.356882	0.039789	8.969	< 2e-16 ***
Drink_score	-0.009734	0.012297	-0.792	0.429
trans:reward	1.798780	0.142900	12.588	< 2e-16 ***
trans:Drink_score	-0.012876	0.008520	-1.511	0.131
reward:Drink_score	-0.010731	0.008058	-1.332	0.183
trans:reward:Drink_score	0.007755	0.030060	0.258	0.796

Signif. codes: $p < .05$ *, $p < .01$ **, $p < .001$ ***

Correlation of Fixed Effects:

	(Intr)	trns	rew	Drnk	trns:rew	trns:Drnk	rew:Drnk
trans	0.149						
reward	0.363	0.203					
Drink_score	0.001	-0.004	-0.006				
trans:reward	0.466	0.420	-0.017	0.003			
trans:Drink_score	-0.003	0.000	0.008	0.156	-0.008		
reward:Drink_score	-0.005	0.007	0.000	0.371	-0.006	0.167	
trans:reward:Drink_score	0.003	-0.009	-0.007	0.467	0.003	0.427	-0.021

A.3.3 Two-Step parameters and intercorrelations of measures of goal-directed/habitual control

Table S 2. Descriptive statistics of 2-Step parameters (n=188).

	β_1	β_2	α_1	α_2	λ	ω	P
1st quartile	2.123	1.700	0.218	0.408	0.236	0.199	0.045
Median	4.554	2.652	0.609	0.630	0.598	0.593	0.099
3rd quartile	7.326	3.741	0.999	0.807	1.000	0.796	0.185

Table S 3. Intercorrelation of measures of goal-directed/habitual behavioral control (n=188).

	ω	MF_{score}	MB_{score}
ω	1	-.090	**.673**†
MF_{score}		1	**-.298**†
MB_{score}			1

Note: † p < .001 (two-tailed). All correlations are Spearman's ρ.

A.3.4 Elastic net analysis

Regression analyses were performed with glmnet (version 2.0-2; J. Friedman et al., 2010) in R (version 3.2.1; R Development Core Team, 2008) with ten 10-fold cross-validations and α=0.5. This level of α was chosen to have a balance between ridge regression and lasso. This approach selects the best predictors of the dependent variable ($Drink_{score}$) with a penalty for the number of predictors, thereby building a parsimonious regression model.

When selecting the model with the least mean squared error, the included variables were the BIS sum score and SURPS Impulsivity subscale (see Table S 4). When applying the "one-standard-error" rule for model selection (cf. J. Friedman et al., 2010) instead, which is more conservative and prefers sparser models, no predictor was chosen (see Table S 4 and Figure S 2).

Table S 4. Coefficients of 17 predictors of $Drink_{score}$ for λ_{min} and λ_{1SE}.

	coef(λ_{min})	coef(λ_{1SE})
(Intercept)	-4.497	-0.463
BIS Sum score	0.071	.
SURPS Impulsivity	0.189	.
ω	.	.
MF_{score}	.	.
MB_{score}	.	.

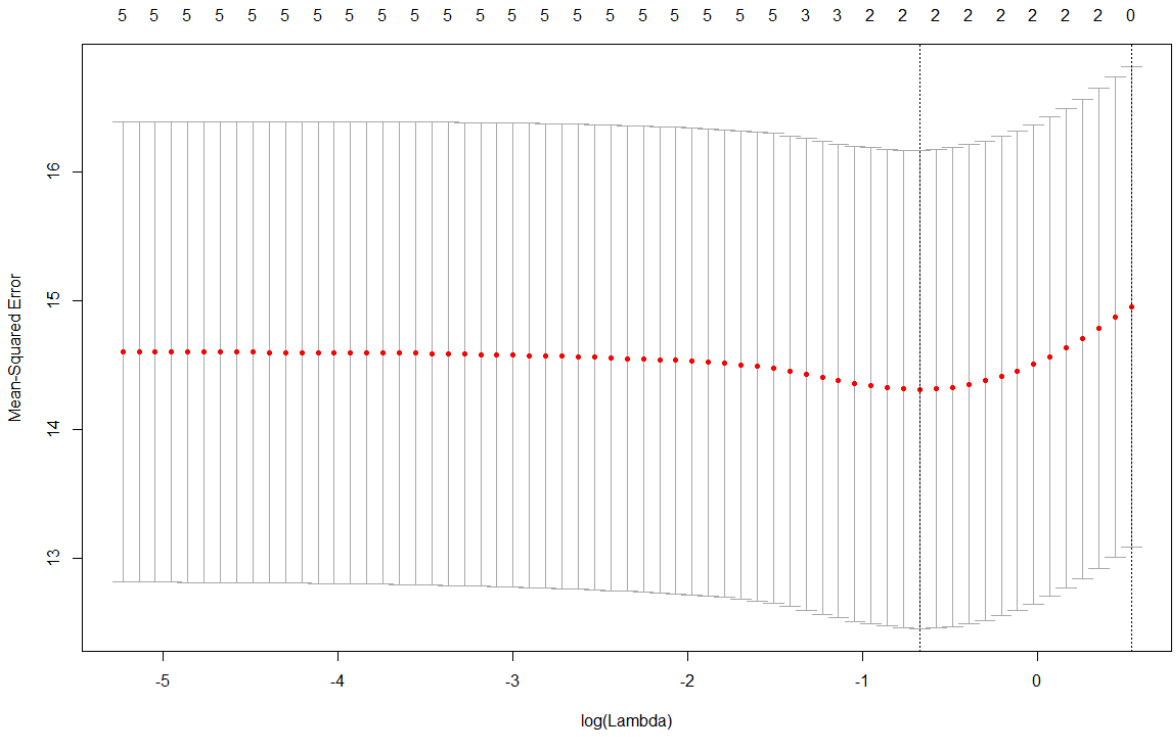

Figure S 2. Mean squared error (MSE) of elastic net model ± standard deviation for different values of log(λ). Digits above figure show included number of predictors. First vertical line from the left depicts the value of λ with the smallest MSE (λ_{min}), second vertical line depicts largest λ within one standard error (λ_{1SE}) which represents the sparser and more conservative model.

A.3.5 Comparisons between binge-drinkers and non-bingers

Table S 5. Results of Exact Mann-Whitney U-tests comparing measures of goal-directedness and drinking behavior between binge-drinkers and non-bingers.

	ω	MF_{score}	MB_{score}	$Drink_{score}$	Age of 1st drink	Age of 1st time drunk	Estimated alcohol consumption in past year (g alc/day)
$N_{non\text{-}bingers}$	49	49	49	49	49	44	49
$N_{binge\text{-}drinkers}$	139	139	139	139	139	136	139
mean $rank_{non\text{-}bingers}$	96.61	84.22	97.10	27.86	109.61	107.50	48.59
mean $rank_{binge\text{-}drinkers}$	93.76	98.12	93.58	117.99	89.17	85.00	110.68
rank $sum_{non\text{-}binge}$	4734	4127	4758	1365	5371	4730	2381
rank $sum_{binge\text{-}drinkers}$	13032	13639	13008	16401	12395	11560	15385
Mann-Whitney-U	3302	2902	3278	**140**	**2665**	**2244**	**1156**
Z	-0.316	-1.537	-0.389	**-9.970**	**-2.349**	**-2.608**	**-6.881**
Exact significance (2-tailed)	.754	.125	.699	**.000**	**.019**	**.009**	**.000**

	Alcohol consumption in past year (g alc/drinking occasion)	ADS Sum Score	OCDS Sum Score	AST	ALT	γ-GT	PEth
$N_{non\text{-}bingers}$	49	48	49	48	48	48	41
$N_{binge\text{-}drinkers}$	139	133	134	135	134	135	117
mean $rank_{non\text{-}bingers}$	44.52	58.29	66.39	96.08	86.33	85.02	73.50
mean $rank_{binge\text{-}drinkers}$	112.12	102.80	101.37	90.55	93.35	94.48	81.60
rank $sum_{non\text{-}binge}$	2181.5	2798	3253	4612	4144	4081	3013.5
rank $sum_{binge\text{-}drinkers}$	15584.5	13673	13583	12224	12509	12755	9547.5
Mann-Whitney-U	**956.5**	**1622**	**2028**	3044	2968	2905	2152.5
Z	**-7.544**	**-5.071**	**-4.014**	-0.622	-0.792	-1.063	-1.049
Exact significance (2-tailed)	**.000**	**.000**	**.000**	.536	.430	.289	.296

A.3.6 Associations between measures of impulsivity (BIS-15) and measures of goal-directed/habitual control and neural correlates thereof

To examine the relationship between impulsivity and behavioral control during the 2-Step task, we correlated our measures of goal-directed/habitual control and λ from the computational model with the BIS-15 subscales and Sum score (λ was the one parameter, where (Deserno, Wilbertz, et al., 2015) found a difference between high and low impulsive participants.) Furthermore, we correlated the BIS-15 with the extracted mean ROI activation in ventral striatum and vmPFC in response to RPE_{MF} and $RPE_{\Delta MB}$. In addition, we examined whether there is a correlation between BOLD response to RPE_{MF} and $RPE_{\Delta MB}$, respectively, and BIS-15 Sum scores in the lateral prefrontal/orbitofrontal cortex, where Deserno et al. had found a group difference using 10mm-spheres around the three peaks of their cluster in the OFC (peak 1: 20|28|-16; peak 2: 38|24|-16; peak 3: 32|42|-14). None of these analyses yielded significant effects. This could be due to the different samples of our study in comparison to Deserno, Wilbertz, et al. (2015): our participants have medium BIS-15 scores whereas Deserno's participants were selected due to their BIS-11 scores to represent extreme groups of the distribution of impulsiveness.

Table S 6. Correlation of BIS-15 subscales and Sum score with behavioral and neural measures of goal-directed/habitual control.

		BIS-15							
		ATT		MOT		NONP		SUM	
		ρ	*p*	*ρ*	*p*	*ρ*	*p*	*ρ*	*p*
λ		.063	.397	.085	.250	-.020	.786	.035	.632
ω		-.016	.826	.042	.571	.001	.995	-.013	.860
MF_{score}		.048	.514	.077	.293	.008	.914	.062	.404
MB_{score}		-.019	.796	.025	.737	.003	.972	-.011	.877
RPE_{MF}	vS	.138	.100	.022	.790	.053	.524	.066	.431
	vmPFC	.089	.291	.057	.496	.063	.452	.115	.172
$RPE_{\Delta MB}$	vS	.042	.619	-.026	.755	.002	.977	-.018	.834
	vmPFC	.000	.998	-.022	.794	.013	.879	-.005	.950

Note: All correlations are Spearman's *ρ*. BIS-15, Barratt Impulsiveness Scale (short form) with ATT, Attention, MOT, Motor, NONP, Non-planning, SUM, Sum score. MB_{score}, score of model-based control. MF_{score}, score of model-free control. ω_{log}, balance between model-free and model-based control, log-transformed. vmPFC, ventromedial prefrontal cortex. vS, ventral striatum.

A.4 Supplementary results - fMRI

A.4.1 Results of fMRI analyses of the main effects of 2Step and the interaction with age of 1st drink

Table S 7. Correlation of BOLD response with RPE_{MF} in whole-brain analyses.

Area	k	T	R/L	x	y	z
Middle occipital gyrus	12830	13.008	R	28	-92	4
Cuneus		10.410	R	20	-94	8
Cerebellum		10.305	L	-34	-74	-20
Nucleus accumbens	4963	12.468	L	-12	4	-10
Caudate nucleus		11.093	R	12	12	-8
Putamen		8.402	L	-28	-12	6
Superior parietal lobule	1729	8.244	L	-34	-64	48
Inferior parietal lobule		8.098	L	-46	-58	50
Inferior parietal lobule		7.925	L	-50	-50	50
Posterior cingulate cortex	700	7.311	L	-2	-30	30
Angular gyrus	1397	6.915	R	36	-64	50
Angular gyrus		6.771	R	50	-58	42
Middle occipital gyrus		4.979	R	32	-68	36
Middle temporal gyrus	190	6.785	R	58	-34	-12
Middle frontal gyrus	491	6.760	L	-42	50	0
Inferior frontal gyrus (p. Triangularis)		6.533	L	-46	46	10
Inferior frontal gyrus (p. Oribitalis)		6.070	L	-44	46	-10
Cerebellar vermis	113	6.212		0	-60	-22
Superior frontal gyrus	190	6.059	R	24	62	0
Middle frontal gyrus		5.709	R	40	56	-2
Inferior frontal gyrus (p. Oribitalis)		4.876	R	48	48	-6
Middle temporal gyrus	43	5.603	L	-52	-40	-14
Middle frontal gyrus	168	5.578	R	36	12	58
Superior frontal gyrus		5.265	R	26	32	54
Middle frontal gyrus		5.136	R	40	24	50
Superior orbital gyrus	52	5.379	R	20	38	-16
Superior orbital gyrus		5.152	R	20	48	-16
Anterior cingulate cortex	72	5.345	R	12	40	20
Insula	25	5.141	R	26	24	-4
Superior frontal gyrus	19	5.092	R	2	26	62
Brain stem	5	4.994		0	-34	-30
Anterior cingulate cortex	16	4.936	R	12	44	2
Superior frontal gyrus	19	4.901	L	-18	28	56
Middle cingulate gyrus	8	4.833		0	-14	32
Precuneus	7	4.762	R	12	-54	40

Note. Displayed at $p_{FWE}<.05$, $k\geq5$, $T\geq4.617$. k is cluster size. T value of peak. R = right, L = left. x, y, z are MNI coordinates.

Table S 8. Correlation of BOLD response with $RPE_{\Delta MB}$ in whole-brain analyses.

Area	k	T	R/L	x	y	z
Caudate nucleus	203	8.913	R	12	10	-8
Putamen	228	8.255	L	-10	10	-8
Inferior parietal lobule	55	5.697	L	-50	-50	52
Inferior temporal gyrus	44	5.331	L	-56	-32	-18
Inferior occipital gyrus	23	5.088	R	30	-88	-4
Medial orbital gyrus	39	5.028	L	-10	44	-6
Middle orbital gyrus	10	5.001	L	-44	46	-8
Medial orbital gyrus	40	4.891	R	6	42	-6
Superior medial gyrus		4.846	R	4	54	2
Superior medial gyrus	8	4.882	L	-10	60	10
Superior frontal gyrus	5	4.860	L	-20	36	50

Note. Displayed at $p_{FWE}<.05$, k≥5, T≥4.617. k is cluster size. T value of peak. R = right, L = left. x, y, z are MNI coordinates.

Table S 9. Results of conjunction analysis of RPE_{MF} and $RPE_{\Delta MB}$ in whole-brain analyses.

Area	k	T	R/L	x	y	z
Caudate nucleus	295	9.826	R	12	10	-8
Putamen	318	9.481	L	-10	10	-8
Inferior parietal lobule	297	6.443	L	-50	-48	52
Angular Gyrus		5.703	L	-40	-70	46
Angular Gyrus		4.988	L	-48	-62	48
Middle temporal gyrus	95	5.749	L	-56	-38	-14
Middle cingulate cortex	65	5.728	R	2	-32	38
Cerebellum	21	5.623	R	42	-62	-42
Middle orbital gyrus	113	5.620	L	-44	46	-8
Inferior frontal gyrus (p. Triangularis)		5.018	L	-40	44	2
Inferior frontal gyrus (p. Orbitalis)		4.901	L	-42	36	-14
Inferior occipital gyrus	59	5.466	R	32	-88	-2
Middle temporal gyrus	26	5.379	R	60	-36	-12
Inferior frontal gyrus (p. Orbitalis)	26	5.331	L	-26	28	-16
Superior medial gyrus	47	5.176	R	8	48	0
Middle occipital gyrus	12	4.959	L	-24	-90	4
Superior frontal gyrus	5	4.920	L	-18	34	52
Fusiform gyrus	26	4.911	L	-34	-76	-14
Fusiform gyrus	12	4.904	L	-30	-52	-16
Inferior occipital gyrus	5	4.780	R	40	-76	-10

Note. Displayed at $p_{FWE}<.05$, k≥5, T≥4.617. k is cluster size. T value of peak. R = right, L = left. x, y, z are MNI coordinates.

Table S 10. Correlation of BOLD response with RPE_{MF} in whole-brain analyses covarying negatively with age of 1st drink.

Area	k	T	R/L	x	y	z
Putamen	472	4.768	R	34	-6	-8
Insula		3.939	R	34	10	-8
Pallidum		3.853	R	20	6	0
Pallidum	608	4.017	L	-14	-2	0
Putamen		3.899	L	-26	-2	4
Putamen/Insula		3.854	L	-40	-20	-10
Superior temporal gyrus	150	3.934	L	-52	-8	-8
Superior temporal gyrus	151	3.870	R	62	-24	4
Superior temporal gyrus		3.818	R	44	-20	0
Superior temporal gyrus		3.411	R	54	-22	6
Anterior cingulate cortex	84	3.870	L	-12	30	18
Anterior cingulate cortex	87	3.858	R	12	32	28
Insula	55	3.837	R	28	28	8
Insula		3.290	R	34	40	0
Inferior orbital gyrus		3.237	R	26	30	0
Middle frontal gyrus	119	3.817	L	-46	38	22
Superior temporal gyrus	64	3.763	R	58	-8	-8
Middle temporal gyrus		3.173	R	50	-8	-16
Supramarginal gyrus	92	3.690	L	-66	-30	28
Supramarginal gyrus		3.445	L	-56	-36	32
Angular gyrus	115	3.643	L	-40	-68	38
Middle occipital gyrus		3.557	L	-34	-70	32
Postcentral gyrus	114	3.613	L	-52	-16	52
Postcentral gyrus		3.606	L	-62	-14	36
Supramarginal gyrus		3.425	L	-54	-20	36
Fusiform gyrus	69	3.511	L	-32	-18	-26
Inferior temporal gyrus		3.460	L	-42	-28	-18
Fusiform gyrus		3.234	L	-34	-28	-22

Note. Displayed at $p_{uncorr}<.001$, $k\geq50$, $T\geq3.148$. k is cluster size. T value of peak. R = right, L = left. x, y, z are MNI coordinates.

A.4.2 Comparisons between binge-drinkers and non-bingers

Table S 11. Results of Exact Mann-Whitney U-tests comparing extracted mean ROI BOLD response between binge-drinkers and non-bingers.

	RPE_{MF}		$RPE_{\Delta MB}$	
	vS	vmPFC	vS	vmPFC
$N_{non\text{-}bingers}$	41	41	41	41
$N_{binge\text{-}drinkers}$	105	105	105	105
mean $rank_{non\text{-}bingers}$	70.78	73.73	78.1	74.76
mean $rank_{binge\text{-}drinkers}$	74.56	73.41	71.7	73.01
rank $sum_{non\text{-}binge}$	2902	3023	3202	3065
rank $sum_{binge\text{-}drinkers}$	7829	7708	7529	7666
Mann-Whitney-U	2041	2143	1964	2101
Z	-0.49	-0.04	-0.82	-0.22
Exact significance (2-tailed)	.630	.969	.414	.825

B Supplementary Information of Study 2

B.1 Computational fits

Besides the abovementioned hybrid model, we fitted two alternative model types to our choice data: 1) a model-free algorithm SARSA(λ), which only captures a main effect of reward on first stage choices and 2) a pure model-based algorithm, which considers the interaction between reward and transition frequencies but does not capture a main effect of reward on first stage choices. The overarching aim of these alternative model fittings was the subsequent model comparison, where we aimed to identify the best fitting algorithm for all groups (healthy controls, abstainers, relapsers). Therefore, we subjected individual model evidences (integrated likelihoods) for all three models to a Bayesian model selection procedure. In line with previous studies (Daw et al., 2011; Deserno, Wilbertz, et al., 2015) the hybrid model was the best fitting model for all three groups (see Figure S 3A and Figure S 3B). Beyond this, we also fitted several other reduced computational models to our data. In our data, the best model fit was always achieved with the original seven parameter model. Simplifications by reducing/ removing particular parameters did not yield more parsimonious fits (Figure S 3C). Moreover, surrogated data generated from the fitted full seven parameter hybrid model captured both the Reward (R) and the Reward x Transition (R x T) effects from the raw behavioral data analyses (Figure S 3D).

B.1.1 Computational fits: between group comparisons and association with other variables

The hybrid model fitted better than chance in 85% of all subjects (143/186). Other studies using young college students did not evidence this large amount of "non-fitting" individuals (Daw et al., 2011; Deserno, Wilbertz, et al., 2015) and we have previously suggested that our comparably low evidence of computational fits might be specific for the here studied age cohort (Sebold et al., 2016) and patient group. Crucially, the proportion of subjects for whom the computational model fitted better than chance was not different between healthy controls, abstaining patients and relapsing patients ($\chi = .89$, $p = .63$, see Figure S 3B). We aimed to further elucidate which variables interfered with computational model fits and focused on demographical and cognitive domains known to interact with model-based or model-free control, namely 1) working memory (Otto, Gershman, et al., 2013; Otto, Raio, et al., 2013; Schad et al., 2014), 2) cognitive speed (Schad et al., 2014), and 3) age (Eppinger, Walter, Heekeren, & Li, 2013). We compared these variables between subjects, whose behavior was fitted better than chance by the computational model and those who were not, by using Wilcoxon rank sum test. We found that working memory capacity was significantly lower in the poor fit individuals (Digit Symbol backwards: $W = 3832$, $p = .01$, $r = -0.18$). This might indicate that sufficient working memory capacity is an essential prerequisite to adequately execute the two-step task. In line with this finding, two other studies have shown, that patients suffering from schizophrenia, who tend to show deficits in working memory capacity (Deserno, Sterzer, Wüstenberg, Heinz, & Schlagenhauf, 2012) also show worse model fits for a computational model-based reinforcement learning model (Culbreth, Westbrook, Daw, Botvinick, & Barch, 2016; Schlagenhauf et al., 2014). None of the other two variables (age: $W = 3259$, $p = .57$, $r = -0.04$ and cognitive speed measured by the Digit Symbol Substitution Test: $W = 3487$, $p = .16$, $r = -0.1$) was significantly different between these two groups.

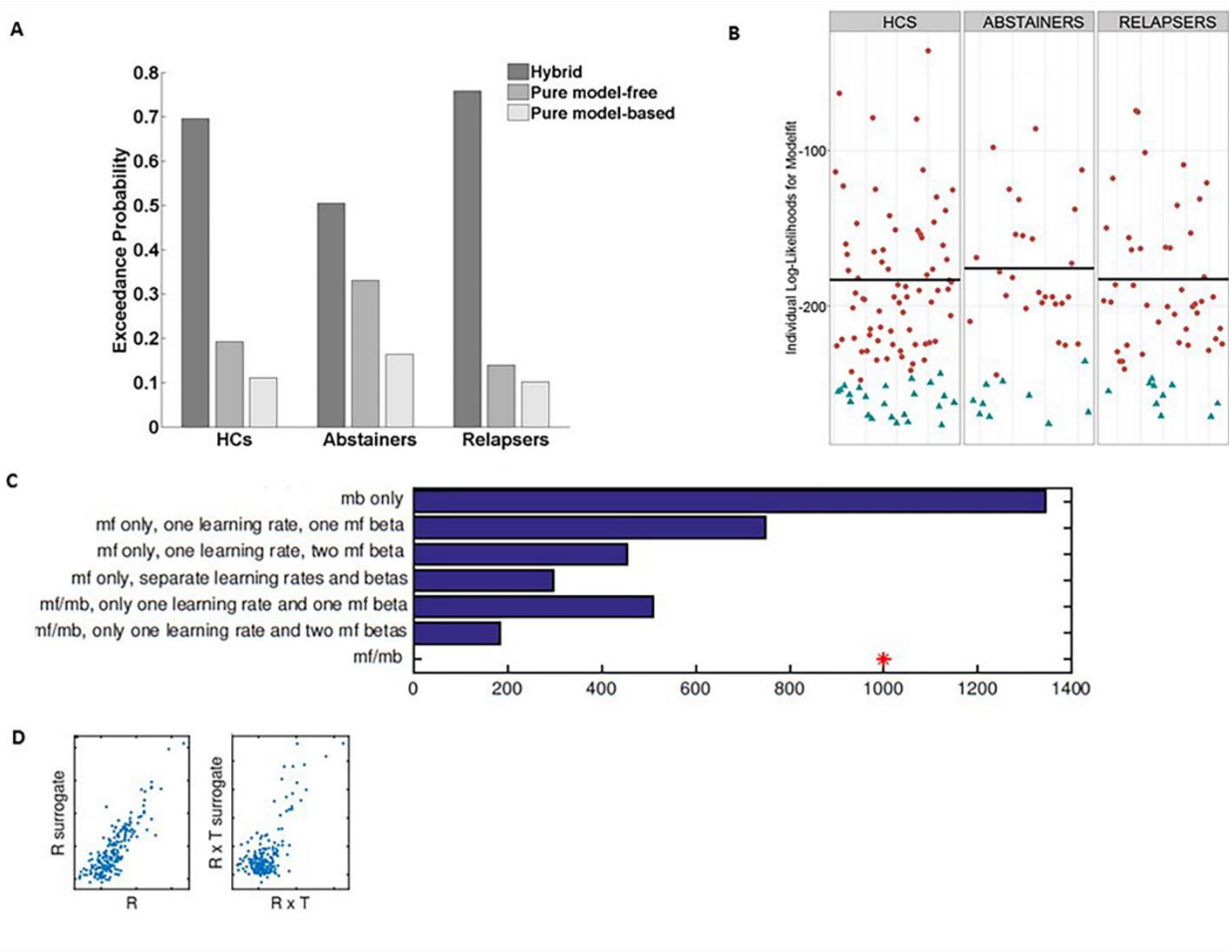

Figure S 3. A: Results from Bayesian model comparison: The final hybrid model was the most likely model for HC (healthy controls), abstainers and relapsers. B: Individual Log-Likelihoods for all three groups. Blue color/triangles indicate individual model fits worse than chance. For further imaging analyses and analyses concerning model parameters, we excluded these subjects. Black solid lines indicate mean log-likelihoods for individuals, who fit better than chance. There were no significant differences between groups in terms of number of subjects who fitted worse than chance. C: Comparisons of model fits for different computational models. The winning model is entitled as mf/mb which is the original seven parameter hybrid model. D: Association between surrogated data from the seven-parameter hybrid model and the model-free and model-based effects from the raw behavioral data analysis.

B.1.2 Between group comparisons of model-parameters from computational model

For exploratory analyses, we also compared all other parameters between groups. Except from a small effect of group on the repetition parameter (ρ, p = .03), which describes general first stage perseveration behavior, we did not see any significant between-group differences in these parameters. Post-hoc analyses demonstrated that abstainers showed stronger perseveration behavior compared to relapsers (p = .008) and trendwise stronger perseveration behavior compared to control participants (p = .05). However, there was no difference between control participants and relapsers (p = .2). Crucially, the effect of group on the repetition parameter (ρ) did not survive correction for multiple comparisons ($p_{Bonferroni}$ < .007).

Table S 12. Mean parameters from the computational model

Inferred parameters from computational model: mean (sd)							
Group	α1	α2	β1	β2	λ	ω	ρ
Controls	0.45	0.50	7.45	3.57	0.58	0.42	0.18
	(0.30)	(0.29)	(4.34)	(2.02)	(0.22)	(0.19)	(0.10)
Abstainers	0.51	0.58	6.68	3.25	0.67	0.44	0.23
	(0.30)	(0.27)	(3.47)	(1.94)	(0.19)	(0.20)	(0.09)
Relapsers	0.43	0.50	7.86	3.55	0.63	0.39	0.16
	(0.37)	(0.32)	(4.42)	(3.17)	(0.21)	(0.24)	(0.12)
F	0.66	0.90	0.66	0.19	1.80	0.51	3.56
p	0.51	0.41	0.51	0.83	0.17	0.60	0.03

B.2 Preprocessing of the functional imaging data

fMRI preprocessing was conducted using Statistical Parametric Mapping software (SPM8; London, UK: Wellcome Department for Imaging Neuroscience) and MATLAB R2014a (Natick, MA: The MathWorks Inc.) and was implemented in Nipype (Gorgolewski et al., 2011). Preprocessing included the following steps: 1) correction for differences in slice acquisition times with reference to the middle slice, 2) realignment of all slices to the first to correct for motion, 3) correction for field inhomogeneities with a voxel displacement map from acquired field maps, 4) coregistration of the mean EPI image to the individual structural MPRAGE image, 5) segmentation and normalization of the individual MPRAGE image to Montreal Neurological Institute (MNI) space and applying normalization parameters to the distortion-corrected EPI images and resampling EPI images to 2 x 2 x 2 mm^3, and 6) spatial smoothing of the EPI images with a Gaussian kernel of 6mm full-width at half-maximum. Prior to statistical analysis, data were high-pass filtered with a cut-off of 128 seconds.

B.3 Exclusion criteria for different analyses

In the imaging analyses we excluded subjects, who did not fit the computational model better than chance (see *Computational fits* section, above). From the remaining 143 subjects, we excluded 6 subjects due to incidental anatomical findings diagnosed by a neuroradiologist. From the remaining 137 subjects excessive head motion (> 3mm translation and 3° rotation) led to exclusion of 14 additional subjects. In 3 subjects coregistration or normalization had failed and in 4 additional subjects significant parts of the ventral striatum (which is a core region involved in this task) were missing due to artefacts.

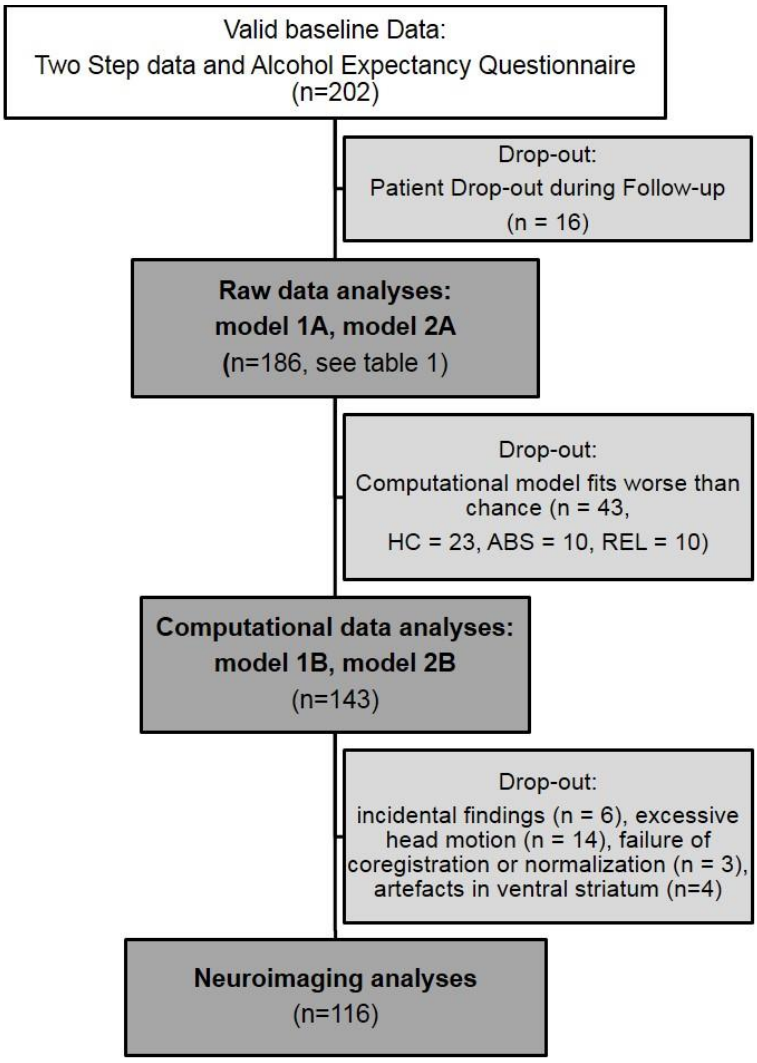

Figure S 4. Description of sample sizes and drop outs at each stage of the analysis procedure. HC = Healthy controls, ABS = Abstainers, REL = Relapsers.

B.4 First level analysis of the functional imaging analysis

We computed RPE_{MF} and $RPE_{\Delta MB}$ for all subjects. These reward-prediction errors are non-zero at two time points: 1) second-stage onsets and 2) outcome presentation. Prediction-errors at second-stage onset compare values of first- and second-stage stimuli and therefore depend on the weighting parameter (ω), which indicates the balance between model-based and model-free decision making. As mentioned in the main text, the two regressors of interest were RPE_{MF} and $RPE_{\Delta MB}$. Just like Daw et al. (2011), the time point of reward delivery was additionally included as a separate regressor and the design-matrix also included first-stage onsets with two parametric modulators, the softmax probability for choosing one of the two first-stage probabilities as well as its partial derivative with respect to ω. The six movement parameters from the realignment were included in the model as nuisance regressors.

B.5 Voxel-based morphometry

Each individual's anatomical T1-weighted image was segmented into three different tissue classes by using the unified segmentation approach, as implemented in SPM 8. Grey matter images were then smoothed by using an isotropic Gaussian kernel (8 mm full-width at half-maximum). Smoothed images were then subjected to a random-effects model containing site and intracranial volume as covariates. We conducted a one-way analysis of variance on smoothed structural images with group as factor (healthy controls, abstainers, relapsers) and site and total intracranial volume as covariates. Mirroring our functional analyses, we performed this analysis by using small volume correction with a mask containing all voxels showing a significant effect for RPE_{MF} and $RPE_{\Delta MB}$ combining all three groups (Figure 9 and Table S 13). This analysis indicated a main effect of group on the mPFC (x = 3, y = 48, z = -9, kE = 374, z = 4.42, p_{FWE_SVC} = .002). Further post-hoc t-tests indicated that group effects in the mPFC were driven by higher grey matter density in control participants compared to relapsers (p_{FWE_SVC} = .002), whereas there was no significant difference between control participants and abstainers or abstainers and relapsers. Performing an additional one-way ANOVA on extracted grey matter densities of the region where we had observed the functional model-based between group differences in the mPFC (peak voxel, x = -16, y = 42, z = -8) again revealed a main effect of group (p = .009). Post-hoc tests indicated larger grey matter densities in control participants compared to abstainers (p = .03) and relapsers (p = .003) whereas there were no differences between abstainers and relapsers (p = .53). Adding these extracted grey matter densities to our functional analyses did not change our observed effects.

Table S 13. Whole brain effects of group on grey matter density at the statistical threshold p < .001, uncorrected that survive FWE correction at the cluster level

Anatomical region	x	y	z	Peak z-value	Cluster (FWE-corr)	Cluster size
Right medial frontal cortex	3	48	-9	4.42	<.0001	2099
Right middle frontal gyrus	5	54	-2	4.29	.022	882
Right middle cingulate gyrus	5	-15	46	4.09	.009	1104

B.6 Drinking Motives Questionnaire

For exploratory purposes, we correlated individual alcohol expectancies with drinking motives, as assessed with the Drinking Motives Questionnaire (Kuntsche et al., 2006), which assesses individual alcohol consumption motives on four scales (Social, Coping, Enhancement, Social pressure/conformity). Across all subjects, each subscale was significantly correlated with the sum score of alcohol expectancies (Social (δ = .5, p < .0001), Coping (δ = .7, p < .0001), Enhancement (δ = .6, p < .0001), Social pressure/conformity (δ = .3, p < .001)), suggesting that each drinking motive was positively associated with alcohol expectancies.

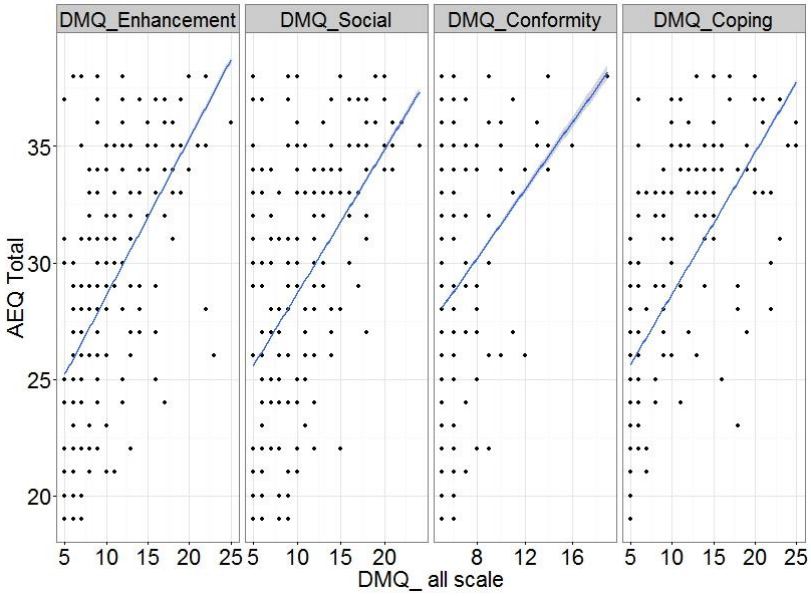

Figure S 5. Association between all four subscales of the Drinking Motives Questionnaire and the sum score of the AEQ.

Similar to the AEQ Score, we found an interaction between group, model-based control and the sum score of drinking motives ($p < .0001$). This time, the association between model-based control and DMQ-scores was absent in control participants ($p = .33$), marginally positive in abstainers ($\delta = .31$, $p = .07$) and again negative in relapsers ($\delta = -.3$, $p = .03$).

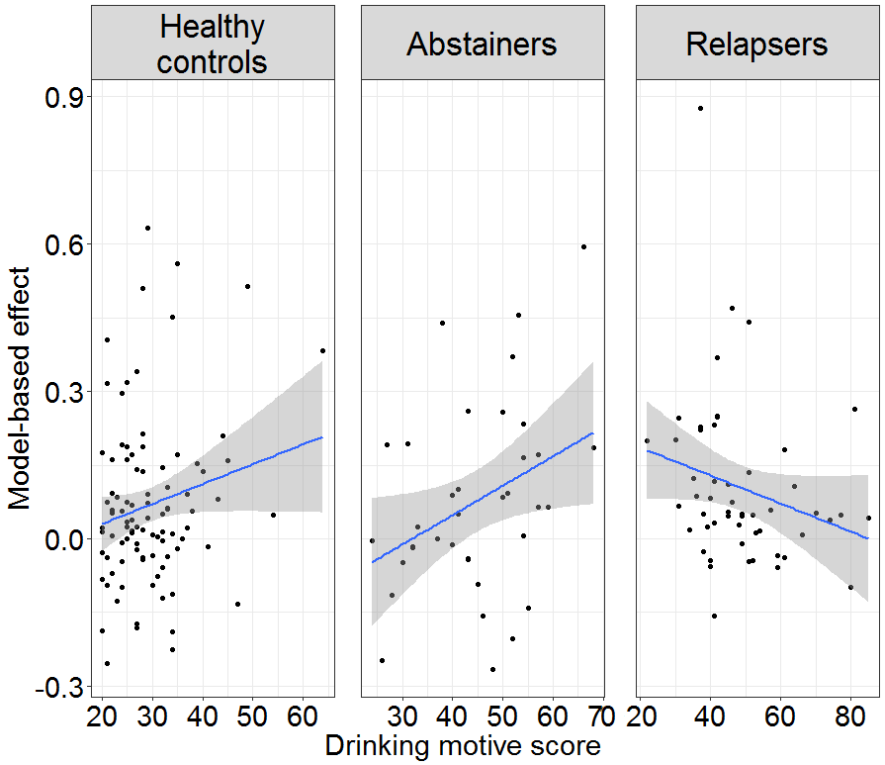

Figure S 6. A model-based strategy usage as a function of drinking motives: Subsequent relapsers showed a negative relationship between Drinking Motives and model-based control. This negative association was not apparent in HCs and marginally positive in abstainers.

Table S 14. Regions that survived the statistical threshold (p < .0001, uncorrected) of the conjunction analysis.

Anatomical region	x	y	z	Peak t-value	Peak (FWE-corr)	Cluster size
Right ventral striatum	12	12	-8	6.38	<.0001	323
Left ventral striatum	-16	8	-10	6.27	<.0001	309
Left medial prefrontal cortex	-8	32	-8	4.85	.017	172
Right inferior occipital gyrus	36	-86	4	4.24	.164	28
Right hippocampus	30	-26	-10	4.03	.312	12
Right anterior cingulate gyrus	2	30	-12	4.03	.314	12

B.7 Model-free comparisons

We additionally asked whether relapsers would show increased correlates of model-free signatures in the mPFC (x = -16, y = 42, z = -8), where we found decreased model-based signatures. However, there were no between group effects neither in whole brain analysis nor by applying a priori region of interest, indicating that group differences were specifically present with respect to model-based decision-making.

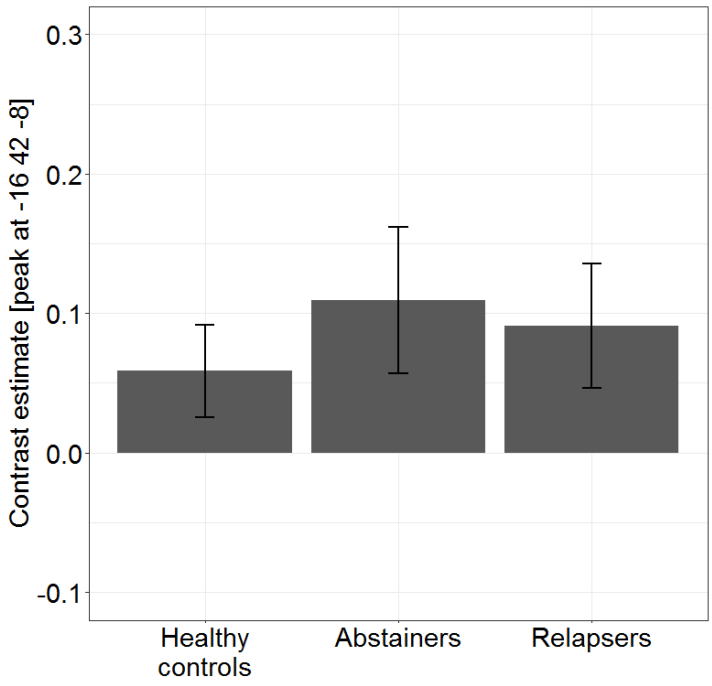

Figure S 7. Model-free estimates from the mPFC (x = -16, y = 42, z = -8) across all three groups. There were no significant between group differences.

B.8 Association with time to relapse

For exploratory purposes, we also assessed whether time to relapse could be predicted from our behavioral data, namely from the interaction between alcohol expectancies and model-based control. More precisely, we assumed that the interaction between AEQ and model-based control in relapsers would show differences with regard to time to relapse. Most patients relapsed within the first three months (Mdn = 63 days). Because of non-normal distribution of the time to relapse variable, we assigned subjects to an early vs. late relapse group (early: within three months (n=30), late: beyond three months (n=19)). Logistic regression, where relapse (early vs. late) was predicted from the interaction between alcohol expectancies and model-based control (analogue to what we conducted with model 2a and 2b), revealed no significant relationship between AEQ and model-based scores (p = .24) for subjects grouped according to early vs. late relapse within the group of relapsers.

B.9 Number of detoxifications and model-based control: behavioral and neuroimaging analyses

As relapsers had reported significantly higher number of previous detoxifications treatments compared to abstainers, we aimed to investigate the association between model-based control and its neural correlates and number of detoxifications in the patient group. Correlational analyses revealed a negative correlation between model-based control and number of detoxifications in the patient group, which closely failed to reach significance (ρ = -.19, p = .07). There was no significant age difference between relapsers and abstainers (abstainers: M = 45.7 years, SD = 12.0, relapsers: M = 45.2, SD = 9.9, p = .82, see Table 4). However, number of detoxifications can be confounded by age. Indeed, in our sample, number of detoxifications was correlated with age (ρ = .29, p = .008). Thus, younger patients had comparably fewer previous detoxification treatments compared to older patients. When we corrected the number of detoxifications for this confounding factor, the previously observed negative correlation with model-based control was far from significant (ρ = -.13, p = .22). On a neural level, we also explored the association between number of detoxifications in the patient group and model-based neural correlates in the mPFC (see Figure 9C). We extracted contrast estimates at the peak level (x = -16, y = 42, z = -8, see Figure 9C), where we had observed between group differences in model-based functional activation and correlated these values with number of detoxifications in the patient group. This analysis revealed no significant association between model-based mPFC activity and number of detoxifications (ρ = -.05, p = .73). Correcting number of detoxifications for age effects did not change this (ρ = .04, p = .74).

C Supplementary Information of Study 3

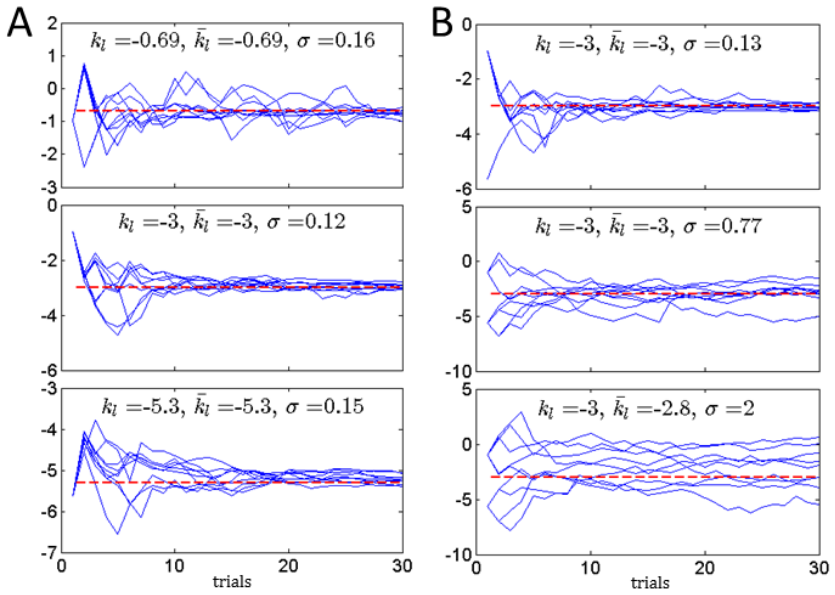

Figure S 8. Simulation of parameter estimates for the case of delay discounting. (A) Different values of $\boldsymbol{k_l}$ *assuming consistent choice behavior* $\boldsymbol{\beta_l = 1.6}$ *are precisely estimated over 30 trials. (B) Estimation of* $\boldsymbol{k_l = -3}$ *over different values of* $\boldsymbol{\beta_l = 1.6; -0.69; -5.3}$. *Every picture represents one simulation and a number of 20 out of 2000 runs are depicted. Dashed lines are the original values of the parameters* $\boldsymbol{k_l}$ *= log(k).*

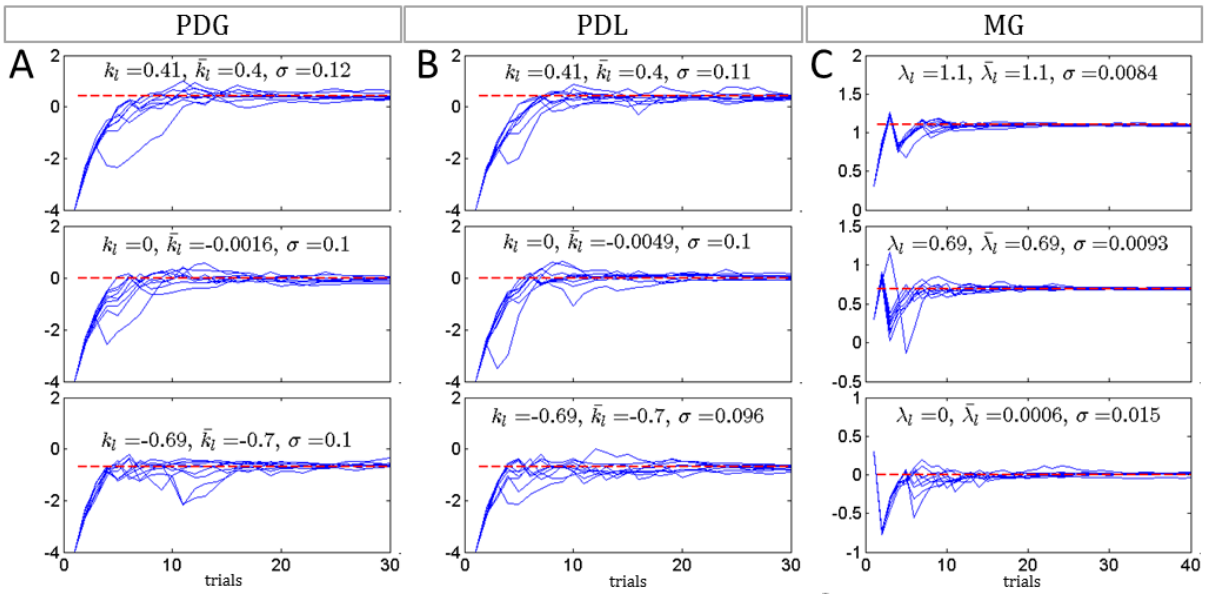

Figure S 9. Simulation of parameter estimates for the case of probability discounting of gains (PDG) and losses (PDL) and for the mixed gambles task (MG). A-C) Simulation of parameter estimates for PDG, PDL and MG respectively. Different values of $\boldsymbol{k_l}$ */* $\boldsymbol{\lambda_l}$ *assuming consistent behavior* $\boldsymbol{\beta_l = 1.6}$. *Every picture represents one simulation and a number of 20 out of 2000 runs are depicted.*

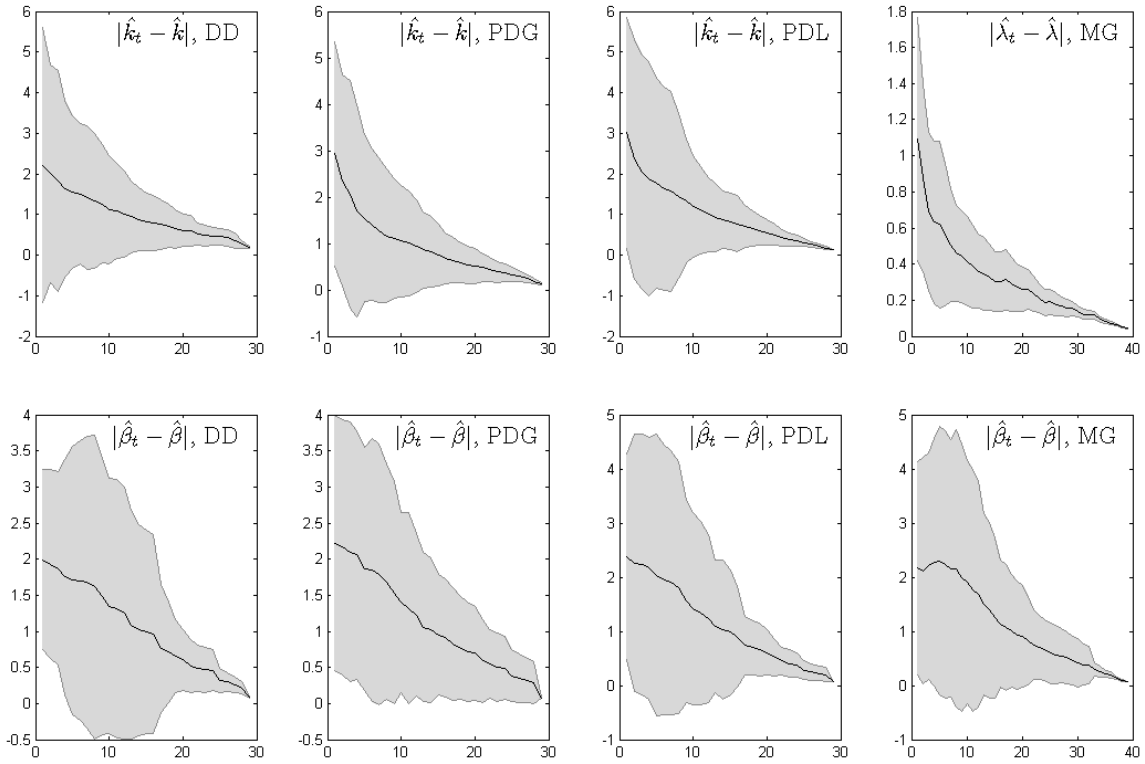

Figure S 10. Convergence of parameter estimation in participant sample data. The average absolute differences between the estimation at each trial and the final estimation for all participants are shown trial by trial by black lines. The gray area depicts the on standard deviation distance from the average. The decreasing pattern in black lines is a sign of convergence and the same for standard deviations means that this is true for the whole group. The top row depicts $|\hat{k}_t - \hat{k}|$ for DD, PDG, and PDL and $|\hat{\lambda}_t - \hat{\lambda}|$ for MG; the bottom row shows $|\hat{\beta}_t - \hat{\beta}|$ for the same tasks.

C.1 Differences between VBDM version used in this study compared to the VBDM version reported in Pooseh et al. (2017)

1. Priors on k and λ:

a. DD: The priors of the log transformed k parameters were normally distributed in the range of
[-15,10] in the version used in this study and were changed to a Beta distribution in the range [-8,2] in Pooseh et al. The range of the prior was shrunk in order to avoid infeasible estimates beyond this range due to the limited offer range.

b. PDG, PDL: The priors of the log transformed k parameters were normally distributed in the range of [-15,10] in this study and were changed to a Beta distribution in the range [-3,3] in Pooseh et al. With this, now the expected value of log(k)=0 (i.e. k=1 as "rational" weighing of probabilities) lies in the middle of the prior range as a kind of baseline.

c. MG: The priors of the (log transformed) λ were normally distributed in the range of [-8,2] in this study and changed to a Beta distribution in the (not log transformed) range [0,4] in Pooseh et al.

2. Priors on Beta:
In this study, priors on β were normally distributed in the range of [-10,10] and were changed to a uniform distribution in the range of [-5,5]. Beyond this range, a change in Beta does not make a big difference.

3. Random offers
In this study, random offers were shown in every fourth trial. In Pooseh et al., this was changed to a random distribution across all trials.

4. Offer range
In this study, the amount of the offered gains and losses in DD, PDG, and PDL ranged from 0.30€ to 10€. In Pooseh et al., the offer range for these three tasks was changed to integers from 3€ to 50€. The offer range for MG is the same in both versions of this task battery (1€ - 40€ for gains and 5€ - 20€ for losses).

5. Feedback
In the experiment versions used in Pooseh et al., it is possible to show the outcome of every trial for PDG, PDL, and MG in terms of winning or losing, so participants get a direct feedback of their choices. There is no feedback implemented in the version used in this study (as is usual in this kind of tasks).

6. Number of trials
In this study, there were 30 trials for DD, PDG, and PDL and 40 trials for MG, which was sufficient to yield stable estimates of the parameters. In Pooseh et al., the number of trials per task was set to 50 to reach even more stable parameter estimation by having more trials to base the estimation procedure on.

C.2 Additional correlational analyses

Table S 15. ***Correlations between behavioral VBDM estimates with themselves, measures of impulsiveness and other personality traits, and alcohol consumption at baseline and the difference to the 12-months follow up in Sample 1.***

	Measure	VBDM							
		DD[a]		PDG[a]		PDL[a]		MG[b]	
		ρ	*p*	*ρ*	*p*	*ρ*	*p*	*ρ*	*p*
VBDM	PDG[a]	-.010	.887						
	PDL[a]	-.127	.079	.000	.998				
	MG[b]	.003	.971	.166	.022	**-.231**	**.001**		
BIS-15	A	.070	.337	-.131	.076	-.067	.360	-.124	.090
	M	.104	.152	-.001	.993	-.117	.107	-.073	.307
	NP	**.216**	**.003**	-.154	.035	.021	.773	-.164	.025
	SUM	**.189**	**.008**	-.121	.096	-.104	.148	-.142	.055
SURPS	AS	-.089	.220	.101	.167	.072	.318	-.020	.789
	HO	.091	.216	-.044	.542	-.001	.993	.160	.027
	IMP	.128	.081	.017	.819	-.061	.405	-.096	.185
	SS	.021	.778	.122	.097	.021	.763	**-.203**	**.004**
Baseline	Age of 1st drink	-.052	.464	.072	.324	-.002	.980	.108	.133
	Age of 1st time drunk	-.073	.320	.155	.036	.079	.271	.099	.191
	Age of 1st binge-drinking event	-.021	.807	-.081	.347	.079	.359	.028	.745
	Est. alcohol consumption in past year (g alc/day)	.038	.595	-.005	.944	.006	.938	-.012	.863
	Alcohol consumption in past year (g alc/drinking occasion)	.050	.487	-.038	.610	-.036	.616	-.002	.980
	Number of binge-drinking events lifetime	.135	.067	-.035	.640	.020	.793	-.047	.528
	Alcohol intake per binge-drinking event (g alc)	**.205**	**.004**	-.001	.982	-.007	.927	-.102	.163
	$Drink_{scoreBL}$	.144	.043	.005	.949	.011	.882	-.042	.562
Δ FU12-BL	ΔEst. alcohol consumption in past year (g alc/day)	-.072	.379	.015	.857	.077	.342	-.008	.919
	ΔEst. alcohol consumption in past year (g alc/day)	-.072	.379	.015	.857	.077	.342	-.008	.919
	ΔNumber of binge-drinking events past year	-.015	.856	.117	.160	-.143	.082	-.057	.505
	ΔAlcohol intake per binge-drinking event (g alc)	-.128	.120	-.054	.505	-.115	.158	.076	.353
	ΔDrinkscore	-.088	.293	-.009	.913	-.065	.428	.032	.690

Note. All reported correlations are Spearman's ρ. P-values are computed using Monte Carlo sampling. Bold printed values survive Benjamini-Hochberg FDR correction. BIS-15 = Barratt Impulsiveness Scale, short form, A = Attentional, M = Motor, NP = Non Planning, Sum = Sum score; DD = Delay discounting; MG = Mixed gambles; PDG = probability discounting for gains; PDL = probability discounting for losses; SURPS = Substance Use Risk Profile Scale, AS = anxiety sensitivity, HO = hopelessness, IMP = impulsivity, SS = sensation seeking; VBDM = value-based decision making.

[a] discounting parameter k_l

[b] loss aversion parameter λ_l

[c] Δ refers to the difference between FU12 and BL data.

Table S 16. Correlations between behavioral VBDM estimates with themselves, sociodemographic data, measures of impulsiveness, and alcohol consumption at baseline in the patients and matched controls of Sample 2.

	Measure	Alcohol-dependent patients (n=114) VBDM								Healthy controls (n=98) VBDM							
		DD[a]		PDG[a]		PDL[a]		MG[b]		DD[a]		PDG[a]		PDL[a]		MG[b]	
		ρ/r	*p*	*ρ/r*	*p*	*ρ/r*	*p*	*ρ/r*	*p*	*ρ/r*	*p*	*ρ/r*	*p*	*ρ/r*	*p*	*ρ/r*	*p*
	SES	-.107	.250	.062	.504	.039	.674	.046	.619	-.023	.833	.088	.413	-.027	.803	-.012	.919
	Smoking status	.143	.128	**-.240**	**.009**	.063	.493	-.072	.436	.136	.194	-.003	.978	.022	.830	-.052	.626
VBDM	PDG[a]	-.093	.332							-.123	.232						
VBDM	PDL[a]	-.092	.335	.143	.130					.013	.898	-.173	.096				
VBDM	MG[b]	-.203	.031	.031	.740	-.036	.702			-.080	.453	**.455**	**.000**	-.162	.115		
BIS-15	A	.068	.488	**-.218**	**.024**	-.008	.934	.002	.984	.021	.830	-.090	.380	-.021	.837	.027	.790
BIS-15	M	-.021	.822	**-.215**	**.023**	.047	.628	.055	.573	.136	.193	-.134	.202	-.070	.495	-.017	.872
BIS-15	NP	.065	.502	**-.262**	**.007**	-.104	.282	-.058	.554	-.021	.839	.010	.928	.070	.493	.038	.493
BIS-15	Sum	.060	.537	**-.296**	**.002**	-.034	.734	.024	.809	.080	.432	-.084	.406	-.003	.975	.039	.701
Baseline	Est. alcohol consumption in past year (g alc/day)	.180	.054	-.082	.381	.019	.840	-.077	.408	.037	.726	-.010	.922	.079	.439	.014	.895
Baseline	Alcohol consumption in past year (g alc/drinking occasion)	.135	.152	-.168	.074	.012	.896	-.046	.623	.152	.141	.019	.855	.051	.617	.003	.980
Baseline	Number of binge-drinking events lifetime	.042	.659	.135	.174	-.185	.060	.027	.782	.092	.377	-.127	.224	.141	.178	-.071	.499
Baseline	Alcohol intake per binge-drinking event in past year (g)	.105	.273	-.187	.044	.017	.854	.034	.714	.110	.285	-.090	.382	.140	.179	-.006	.954
Baseline	Cumulated lifetime alcohol intake (kg)	.016	.861	.023	.801	-.214	.020	-.070	.452	-.018	.866	-.140	.172	-.046	.657	-.015	.885
Baseline	ADS sum score	-.050	.594	-.141	.130	.043	.645	-.049	.602	.085	.415	-.075	.472	.022	.035	-.130	.212
Baseline	OCDS-G total score	.026	.789	-.019	.840	-.093	.334	-.172	.070	.017	.876	-.046	.662	.006	.949	.039	.709

Note. All reported correlations are Spearman's ρ except for correlations with dichotomous smoking status, which are point biserial correlations r. P-values are computed using Monte Carlo sampling. Bold printed values survive Benjamini-Hochberg FDR correction. ADS = Alcohol Dependence Scale; BIS-15 = Barratt Impulsiveness Scale, short form, A = Attentional, M = Motor, NP = Non Planning, Sum = Sum score; DD = Delay discounting; MG = Mixed gambles task; OCDS-G = Obsessive Compulsive Drinking Scale, German version; PDG = probability discounting for gains; PDL = probability discounting for losses; SES = socioeconomic status; VBDM = value-based decision making.

[a] discounting parameter k_l

[b] loss aversion parameter λ_l

D Supplementary Information for additional analyses

I have performed additional analyses that were not part of the published worked, but aid in answering the research questions presented in this thesis. For that purpose, I first analyzed the one-year predictability of drinking trajectories in our sample of young adult social drinkers (Sample 1) with Two-Step task behavior equivalently to the prediction of drinking trajectories with choice biases towards delays, risks, and valence in Study 3. These analyses revealed no significant results. Baseline model-free control was not associated with the level of general drinking behavior at the 12-month follow-up assessment (MF_{score} x $Drink_{scoreFU12}$: Spearman's ρ = -.130, p = .114) or the change of drinking from baseline to follow up (MF_{score} x $\Delta Drink_{score}$: Spearman's ρ = -.080, p = .334), and neither were model-based control (MB_{score} x $Drink_{scoreFU12}$: Spearman's ρ = .069, p = .401; MB_{score} x $\Delta Drink_{score}$: Spearman's ρ = -.003, p = .975) nor the computational parameter indicating the balance between model-free and model- based control (ω_{log} x $Drink_{scoreFU12}$: Spearman's ρ = .080, p = .336; ω_{log} x $\Delta Drink_{score}$: Spearman's ρ = .094, p = .257). These results complement the previous findings and complete the investigation of goal-directed and habitual control with current and future drinking behavior in social drinkers and AUD patients.

Second, I examined the correlations between model-free and model-based control in the Tw-Step task (Study 1) with the four VBDM parameters (Study 3) in the young-adult sample. None of these correlations reached significance (Table S 17).

Table S 17. Correlation between measures of model-free and model-based control and VBDM parameters.

		VBDM			
		DD log(k)	PDG log(k)	PDL log(k)	MG log(λ)
MFscore	Spearman's ρ	.004	.066	-.069	-.104
	p	.960	.373	.345	.165
MBscore	Spearman's ρ	-.142	.016	.092	.030
	p	.061	.825	.211	.687

Note. P-values were computed with Monte Carlo simulations of 10,000 samples.

Danksagung

Diese Arbeit ist nicht nur das Resultat vieler Arbeitsstunden, sondern auch der Unterstützung sehr vieler Menschen, ohne die sie nicht möglich gewesen wäre.

Allen voran danke ich meinem Betreuer Michael Smolka für viele aufschlussreiche Diskussionen, fachliche Unterstützung und die langjährige konstruktive Zusammenarbeit und Shu-Chen Li dafür, dass sie sich zur Begutachtung meiner Dissertation bereit erklärte.

Zusätzlich danke ich allen meinen Kollegen, sowohl den SeSyNs als auch den Mitarbeitern der Forschergruppe, für viele Jahre gemeinsamen Arbeitens, Lachens und Leidens.

Schlussendlich gibt es noch unzählige Menschen, die mein Leben neben der Arbeit bereichern, meine Familie und Freunde. Ich danke euch von Herzen für alles, was ihr in den letzten Jahren für mich getan und mit mir durchgestanden habt. Ohne euch hätte ich es definitiv niemals geschafft.

(Ich verzichte absichtlich auf das Nennen von Namen in den letzten beiden Absätzen, weil ich sonst mit Sicherheit einige vergessen würde zu erwähnen, die es auf jeden Fall verdient hätten, erwähnt zu werden. Aber ich gehe davon aus, dass ihr schon wisst, wenn ihr zum Kreise derer gehört, denen ich an dieser Stelle danken möchte. ;))

Erklärungen

Hiermit versichere ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht. Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt. Es haben bisher keine erfolglosen Promotionsverfahren des Promovenden stattgefunden.

Die Promotionsordnung der Fakultät Mathematik und Naturwissenschaften der TU Dresden vom 23.02.2011 (zuletzt geändert am 18.06.2014) erkenne ich an.

Ein Führungszeugnis zur Übersendung an die Fakultät Mathematik und Naturwissenschaften der TU Dresden, Fachrichtung Psychologie, z.Hd. Frau Petra Freitag, wurde am 29.08.2017 beantragt.

Diese Dissertation wurde während meiner Tätigkeit in der Abteilung Systemische Neurowissenschaften der Klinik und Poliklinik für Psychiatrie und Psychotherapie, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden unter der Betreuung von Prof. Dr. med. Michael N. Smolka angefertigt zur Einreichung an der Fachrichtung Psychologie, Fakultät Mathematik und Naturwissenschaften der TU Dresden.

Stephan Nebe Dresden, den 07.09.2017